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THE CAUSES AND EVOLUTION OF
CORONARY OBSTRUCTION*

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OTHER GROSS Lecturers, dealing with their own original observations, have brought out various aspects of our knowledge of coronary disease. For an internist who has made no such contribution, this may be a proper moment to review the problem once more. As a text, a timely statement by a young Montreal doctor will be used.

"In the worry and strain of modern life arterial degeneration is not only very common, but develops often at a very early age. For this I believe that the high pressure at which men live is responsible, rather than excesses in eating and drinking." This statement of William Osler, made in 1896, is echoed vigorously by Russek and by Friedman in 1960. Osler later noted that coronary disease was rare in the wards or necropsies of large city hospitals, but common in private practice, and that most of his patients were men who "eat, drink and smoke to excess". This also has been fully confirmed. The study of smokers, undertaken to cast light on cancer of the lung, has shown that most of the excessive death rate in smokers is due to coronary disease. Many studies have emphasized the importance of diet, and Amatuzio has reported patients whose plasma lipids rise markedly on even moderate intake of alcohol. Osler also stressed hereditary influences and gout. It is now known that elevated urate levels have about the same significance as elevated plasma cholesterol levels in separating coronary suspects from controls. Osler differed from most modern writers on coronary disease in that he did not ascribe it to a single cause.

For thousands of years physicians believed that disease developed as a result of the combined force of many factors. Arabic, Jewish and Christian doctors all considered the constitution of their patients, the influence of planets and constellations, and the nature of the region and its climate when they discussed the causes of epidemic disease, or the nature of any patient's disorder.

After the rise of chemistry and bacteriology during the nineteenth century, this old multifactor notion of disease yielded to a new concept—"one disease—one cause". Almost lost to sight was the subtle interplay of many influences which actually determine the manifestations of most illnesses. At the height of their unitarian pride, physicians scoffed at the previous generation for having ascribed phthisis to disappointment in love or thwarted ambition, and for having blamed tabes and paresis on intense intellectual or commercial activity.

The primary cause of disease can be defined as that factor the absence of which prevents disease, no matter how strongly all other factors may act. Thus, diets rich in ascorbic acid prevent scurvy, an environment free of tubercle bacilli prevents tuberculosis, no matter how poorly nourished, overworked, homesick or ambitious for glory a person may be. The student of coronary disease asks himself, "Is there a primary cause? What is the relative importance of each causative factor?"

Some students of the problem of arterial obstruction offer theories of pathogenesis which ignore causation entirely. Thus Winternitz' hypothesis that it is all due to intimal hemorrhage, and the old, but often revived, theory that it is all due to mural thrombosis, do not offer any explanation of why intimal purpura or thrombosis should occur in the first place, or why certain arterial sites, certain families, or even certain large populations are predisposed, and others almost immune, to arterial occlusion. The weakest point of these theories is that they imply defects in the arterial intima to initiate such intimal bleeding or clotting, but offer no hint as to what these defects may be, how they can be evoked experimentally, or why they occur in well-nourished people with no avitaminosis or unusual vascular stresses and are rare in undernourished people forced to maintain high rates of blood flow by long hours of hard work.

Venous thrombosis and atherosclerosis are both favoured by diets rich in saturated fats and by stresses which cause hyperlipemia. But veins never develop atheromas, and in spite of the slow flow in veins as compared with arteries, spontaneous thrombosis on walls of veins rarely occurs. Injury from pressure on the veins in the calves, thighs, and buttocks (invisible bed sores) initiate throm-

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botic disease in most cases, but some thrombi result from phlebitis or cancer implants. In arteries, with more rapid flow, thrombi also occur only at sites of injury, most frequently injury resulting from the reaction to atheromas. Venous thrombi organize into fibrous scars, free of lipid and foam cells, since venous pressure is too low to force lipid-rich plasma filtrate into the wall or into the clots. In the arteries, organizing thrombi are favourite sites for atheroma formation.

Recent studies of the evolution of arterial disease have clearly shown that intimal purpura and mural thrombosis are not early features of atherosclerosis. Lober,¹ studying coronary arteries from infancy to senility, and the late Russell Holman,² examining aortas from childhood into maturity, have found that progress of plaque formation is most rapid during rapid growth—in the suckling and in the adolescent. At such times, thrombogenesis in veins, arteries or the atria is minimal, and the early lesions show no evidence of intimal hemorrhage or of mural thrombosis. Bragdon³ found that suckling rabbits all had lipid deposition in the aortic intima, so that the situation in man is not unique. While most important in the later stages of arterial obstruction, hemorrhage and thrombosis need not be considered as factors initiating a disorder evident grossly in half of American men by the time they are old enough to vote.

The fact can not be too strongly emphasized that atheromas form swiftly in the succulent, swiftly growing tissues of babes and adolescents, even though their plasma lipid levels are relatively low. They form relatively slowly in the drier, denser and degenerating arterial walls of adult or senile people. Slow accretion, fibrosis and thrombosis, not rapid deposition of lipid in the intima, characterize atherosclerosis after maturity. Yet exceptions are not rare. Coronary thrombosis can occur in young men, even with blood cholesterol levels under 160 mg. per 100 ml., and elderly persons with hypercholesterolemia often die with no evidence of old or fresh thrombi but with large myocardial infarcts and an extremely atheromatous intima.

Before considering the general causes of atherosclerosis and arterial thrombosis, some note should be taken of the localization of atheromas. In subjects who have no evidence of disease elsewhere, even in tissues of the same organ or system, it is striking to see tuberculosis progressing only at the apices of the lungs, syphilis destroying the media only in the ascending part of the aorta, or atherosclerosis demonstrable only in the coronary arteries. Nothing proves more clearly that even when a specific cause for a disease is present, its ability to damage the tissues may be very sharply limited. The localization of syphilis in nervous or vascular tissues remains a profound mystery; the vulnerability of the apices to phthisis has been explained, and some light can be shed on predilection of atheromas for various sites in the body.

Spalteholz⁴ re-emphasized the fact that the intima of the large coronary arteries is unlike that of other arteries of the same calibre elsewhere in the body. In cross sections, there are cushions of intima formed by spiral struts of loose collagen about longitudinally oriented smooth muscle. These vary in number and in size in different subjects; even at birth they are more striking in males. Such structures probably account for the predisposition of the coronary arteries to the intimal deposition of lipid. Familial differences and sex differences in size of intimal struts may be important in determining the tendency to precocious coronary disease in males and in certain families.

There is abundant evidence that intimal thickening, at points where branches come off larger vessels or at sites of medial injury due to aortitis syphilitica or to periarteritis, permits atheroma to develop while adjacent arterial segments with thin intimal layers remain free from lipid deposition. Hydraulic stresses due to vibration or eddies and degenerative changes in the media also lead to local intimal thickening. The innate coronary intimal cushions offer a special case of the general phenomenon that atheromas appear first where the intimal layers are thickest. Since the atheroma itself causes further thickening, a vicious circle is started which may end in ulceration and thrombotic occlusion, or in almost total occlusion by atheromatous plaques.

The level of arterial pressure, in any given artery, also affects rates of atherogenesis. In animal experiments, hypertensive dogs, rabbits or chickens develop atherosclerosis more rapidly than normotensive controls on the same diet and cholesterol intake. In man, pulmonary atheromas are rare in most patients with severe systemic arterial disease, but pulmonic hypertension often is associated with marked atheroma formation in large and small pulmonic arteries. Atheromas are far more abundant in arteries of the legs, subjected to considerable hydrostatic pressure, than in the corresponding vessels of the arms, where gravity acts less effectively to raise blood pressure.

The nearest one can come to a primary feature of atherogenesis and of thrombogenesis is an abnormal state of the plasma lipids related to the diet. The observations of Dedichen⁵ in Oslo first proved that the incidences of thromboembolic disease of veins and of myocardial infarcts fall and rise together when the animal fat of a population is reduced and then replaced. Thomas⁶ data on matched autopsies of people over 40 revealed that the incidence of either disease is under 2% in Uganda, and over 20% in Missouri. Thomas had previously shown that lysis of pulmonary emboli is prevented in rabbits with hyperlipemia. He noted that coronary and renal artery thrombosis occurs in rats on cholate-cholesterol-thiouracil regimens, causing hyperlipemia if the fat in the diet is butter, and not, if it is corn oil.⁷ Retardation of clot lysis by high fat meals and some acceleration of clotting

(revealed only by special techniques) can be demonstrated in man.^{8,9} Thus, there is experimental as well as clinical and necropsy evidence that disturbances in plasma lipid, which only cause atheromas in most animals and in young humans, may accelerate clot growth or retard clot lysis and lead to arterial or venous thrombosis under special experimental conditions and in ageing men and women.

The abnormality of plasma lipid that seems most closely related to atherogenesis is a rise in cholesterol, and particularly of the fraction bound to beta lipoprotein. The fraction bound to lecithin-rich alpha lipoprotein, and elevated in obstructive jaundice, stabilizes all plasma lipids and retards atheroma formation. Diets rich in animal fat raise beta lipoprotein, total cholesterol and triglyceride levels in the plasma. Replacement of such fat by corn oil reduces all these elements; the drop in triglyceride is usually more striking than that in cholesterol in those whose triglyceride elevation is most marked.¹⁰ In persons on low fat diets, cholesterol levels tend to fall, but triglycerides may rise in those in whom these levels are initially high.

In men with myocardial infarction, the average triglyceride levels are more elevated in relation to controls of the same age than are the cholesterol levels.¹¹ It seems probable that high triglyceride levels, and high content of chylomicra in the plasma, have more to do with thrombogenesis than the levels of cholesterol and its various fractions. While all the influences—dietary, endocrine, emotional, or hereditary enzyme defects—which elevate the plasma cholesterol level also raise triglyceride, the individual variation in response of these lipids is extremely variable. In women cholesterol elevation is more marked; in men, triglyceride in those with abnormally high levels of plasma lipid.¹⁰

It must be emphasized that in man and the dog, cholesterol levels in plasma are far more sensitive to the type and quantity of fat ingested than to the cholesterol in the diet. In rabbits and chickens, the reverse is true. But since many high cholesterol foods are rich in saturated fat, and most sources of unsaturated fat are low in cholesterol, or are cholesterol-free, the human populations who have a low cholesterol intake are all taking diets low in saturated fats.

Alcohol behaves like saturated fat in studies of hyperlipemic subjects.¹² Cholesterol-free vegetable oils, such as coconut oil, which are highly saturated, also raise the plasma cholesterol level when ingested daily.¹² Unsaturated fatty acids lower plasma cholesterol by increasing the hepatic degradation of cholesterol to bile salt.¹³ Raising the degree of unsaturation or the quantity of a given unsaturated fatty acid in the diet causes higher rates of bile acid and lower rates of cholesterol excretion in bile.¹⁴ Thus less cholesterol is available for reabsorption and more is degraded to cholate.

Plasma lipid levels are thus strongly influenced by dietary composition. The low incidence of cholesterol gallstones, coronary disease, and postpartum or postoperative thromboembolism, which Snapper¹⁵ noted as characteristic of oriental races living on diets free of milk products and low in eggs and meat, is probably due to dietary, not to genetic influences. The blood cholesterol levels found in such countries average under 160 mg. per 100 ml., while people of the same races living in America or Holland, on the usual diets of these countries, have levels equal to Caucasians taking the same diets (250 mg. per 100 ml.).¹⁶ Thus it seems perfectly reasonable to conclude that the primary factor in coronary artery obstruction and in thromboembolic disease is a diet rich in foods peculiar to a small but prosperous fraction of the human race.

This hypothesis is not yet established and is rejected by many investigators. It has not been proved that diets free of eggs and milk products, low in saturated fatty acid and with 20% of calories from polyunsaturated fatty acid will give total protection to 100% of the human race. A few atheromas may occur in aged animals, birds and human beings on such biologically normal diets, and some families have hypercholesterolemia and hyperlipemia in spite of the most meticulous dietary control. In such families, as in many diabetics, cholesterol and saturated fat synthesis are rapid even when they have diets low in calories and saturated fats, and cholesterol excretion into the duodenum is high. As a result the plasma lipids may be more abnormal than those in many patients with coronary disease who live on diets rich in animal fat. For, at the time infarction occurs, in a few patients plasma cholesterol may be under 200 mg. per 100 ml. and triglyceride levels may be only moderately elevated.

While conceding the possibility of coronary obstruction after a lifetime on a diet low in saturated fat and adequate in unsaturated fat, one must hasten to emphasize that for more than 95% of the human race, high animal-fat intake has the same relation to coronary obstruction and postoperative thromboembolism as the tubercle bacillus to apical tuberculosis. Most of a population exposed to tubercle bacilli will develop skin sensitivity and no active disease; most of those on American diets will have no myocardial infarction or thromboembolism although they nearly all have atheromas. In tuberculosis and in coronary disease, familial susceptibility is striking and diabetes greatly lowers resistance to both. When populations were heavily exposed to tubercle bacilli in the urban society of the eighteenth and nineteenth centuries, physicians and laymen considered the disease not a contagion, but the result of overwork, intense ambition, frustration and emotional stress of all sorts.

Where a high animal-fat diet has been available—that is, for most North Americans since 1920, for

prosperous Europeans for several centuries, and for the rich in many poorer lands today—coronary disease very often seems due to intense ambition and, as Osler put it, "the habit of working the machine to its maximum capacity". Perhaps frustration and misdirected energy is more important,¹⁷ for in both insurance and telephone employees the age-corrected incidence of infarction is lowest in executive personnel, highest in the clerical force.¹⁸

The mechanism through which stress, in our well-nourished population, affects plasma lipid levels can now be described. Fat-mobilizing hormone from the pituitary and adrenal corticosteroids which raise lipid levels apparently are released in response to nervous stimuli. Catecholamine production is said to rise during daily activity to higher levels in men prone to coronary disease than in controls.¹⁹ This also could cause elevation in plasma lipid levels. A rise in lipid levels was noted in 1931 in cats roused by barking dogs, and has frequently been noted in men anxious because of college examinations.²⁰

There is reason to believe that such a rise in blood lipids during periods of annoyance or anxiety is much greater in hyperlipemic individuals than in controls, and in the former the rise is apparently much less when the diets are low in animal fat. Brown and Page found that blood cholesterol levels of a normal group, tested at weekly intervals for over four years, never varied more than 25 mg. per 100 ml. of plasma from the mean value. They noted similar fixed levels in most patients with hypercholesterolemia who had a low fat diet. In these patients variations of blood cholesterol of over 100 mg. per 100 ml. occurred when the diet was uncontrolled, but less than 15 mg. from the mean when the diet contained vegetable oil.¹⁰

This evidence of stabilized low plasma lipid levels in patients with hyperlipemia who are kept on diets low in animal fat, as contrasted with wide fluctuations at a higher level when on the usual American diet, may explain why other populations living on diets of cereal and beans show no evidence of hyperlipemia due either to inherited metabolic defects or to periods of intense emotional stress. Snapper,¹⁵ and other physicians at Pekin Union Medical School during a period of great financial and social stress for the native population, noted that peptic ulcer, that classic example of psychosomatic disease, was as frequent as in America. Yet low blood cholesterol levels and almost complete freedom from myocardial infarction and thromboembolism were noted at that time. The decline in infarction and embolism noted by Dedichen in Nazi-held Oslo was associated with a great increase in anxiety, fear and frustration in the population.

All this leads one to believe that neither hereditary metabolic traits, nor inherited or acquired traits of personality will cause hyperlipemia or coronary disease in the vast majority of human

beings if they have diets normal for anthropoids and man. However, with our usual diets, there is no doubt that Osler was right, and coronary disease favours men "leading lives of high tension, who smoke and drink to excess".

In postmortem studies of people older than 50 thrombosis is found much more frequently in those with myocardial infarction, but aortic and even coronary atheromas are only slightly more severe in these persons than in others. Many who have died of coronary artery disease show fewer atheromas than men of the same age free of coronary thrombosis. With advancing age the levels of fibrinolysin and of heparin-like material in the plasma tend to decline and this lack of protection from thrombosis has been noted in coronary patients even more than in controls of the same age.²¹ Such a decline in levels of antithrombotic enzymes may well account for the increase in arterial as well as in venous thrombi in older people in our population, surfeited with animal fat. It would also explain the predominance of the thrombotic, rather than of the atheromatous manifestations of hyperlipemia, especially in men with high blood triglyceride levels, as a population ages.

We come last to the mystery of the relation of sex to coronary disease. Certainly there is no lack of explanations for male predominance.²² Men have more and larger intimal cushions, even at birth. Estrogens lower beta lipoprotein levels and raise those of the protective alpha lipoproteins. During adolescence, white girls eat much less animal fat than boys, and it is only at this age and in white girls that atherogenesis proceeds more slowly than in males. In Negroes, aortic atheromas develop quite as fast in adolescent females as in males, and the age at death from coronary disease is quite as early in the female of this race. Schopenhauer wrote that "feminine mystery is a screen with nothing behind it". The difference in age at death of white men and women who succumb to coronary disease is very striking, but it seems to be an enigma for which there are many explanations, with a most mysterious exception involving the entire Negro race. An explanation of this exception will clarify which factors are of real importance in protecting the white female from coronary death for 10 or 15 years longer than the male.

One wonders what would happen if white boys, especially in families prone to coronary disease, could be offered appetizing, high vegetable fat, high protein diets before adolescence, and given a distaste for those baby foods—milk and eggs. They might well survive free of coronary disease longer than their spouses, even though they smoked and drank more and were driven by demons of ambition, curiosity, and perfectionism. Some of us, when we experience our first coronary symptoms, fervently wish our patients had known about this possibility and had followed John Hunter's advice, "Don't think! Try the experiment!"

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RADIOACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM

EXPERIENCE AT THE TORONTO GENERAL HOSPITAL, 1950-58*

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PART I‡

THE PURPOSE of this paper is to review the experience of the authors with I^{131} in the treatment of hyperthyroidism; the review encompasses the first eight years of use of this isotope after its introduction by one of us (M.W.J.) in the Toronto General Hospital in 1950.

The history and rationale of the use of radioactive iodine in the investigation and treatment of thyroid disease have been amply discussed in several recent publications and textbooks,¹⁻⁶ and thus will be only briefly outlined in this report. It is apparent that an intelligent approach to an understanding of the use of radioactive iodine in diagnosis and therapy must be predicated upon a clear understanding of thyroid physiology in normal and abnormal states, and the role that iodine plays in thyroid function.

IODINE CYCLE

In areas of adequate iodine supply, the adult ingests about 125 to 150 μ g. of iodine daily,^{5,7} and

excretes a similar quantity, so that iodine equilibrium is maintained. Only that part of ingested iodine which is in the form of iodide, or can be converted to iodide, is available for physiological use. The conversion of iodates or iodine to the iodide form generally occurs within the gastrointestinal tract, but may also occur elsewhere by enzymatic reduction. Inorganic iodide is present in the extracellular fluid in trace amounts (in the order of 3.0 μ g. per litre), and is actually in fairly uniform concentration throughout the body water (iodide space).⁸

The thyroid gland is (with the partial exception of the gastric mucosa and salivary glands) virtually the only organ in the body which is capable of selectively removing the iodide from the blood stream and concentrating it to many times its plasma concentration. This "trapping" is under enzymatic control and TSH stimulation. The trapped iodide is rapidly converted to protein-bound iodine by mechanisms which are also controlled by specific enzymes. Since the actual production of thyroid hormone need not concern us here, the reader is referred to excellent reviews of this subject reported elsewhere.^{9,10}

It is important to note that the total amount of hormone secreted per day in normal persons has been estimated to contain approximately 70 μ g. iodide.⁵ In the periphery, the hormone is degraded and its iodine content set free as inorganic iodide, which again enters the body iodide pool and is available for use in the same manner as ingested iodide. Excretion of iodide is almost entirely by way of the urine, with trace amounts in sweat and feces. Iodide is also found in breast milk.

A recent study of the quantitative phenomena of stable iodine metabolism has been made by Riggs,⁷ and is here tabulated (Table I).

It is noteworthy that iodide is concentrated in the saliva and gastric secretions, but as the chemical form of the iodide is not changed, and as these secretions do not leave the body but are reabsorbed completely, the iodide re-enters the body iodide pool.³ This concentration of iodide by the salivary glands and gastric mucosa is of no physiological

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‡This is the first of three instalments in which this paper is being published. The complete bibliography will be published with the final instalment of this report.

TABLE I.—QUANTITATIVE DATA ON IODINE METABOLISM IN MAN*

	Units	Normal	Hyper-thyroid
Rate of secretion of hormonal iodine.....	µg./day	70	597
Daily intake of iodine.....	µg./day	150	250
Daily urinary excretion of iodine.....	µg./day	144	199
Daily fecal excretion of iodine.....	µg./day	6	51.1
Total iodine in iodide space (inorganic).....	µg.	75	103
Total iodine in thyroid gland (organic).....	µg.	8000	5500
Total iodine in organic pool (extrathyroidal).....	µg.	1200	3360
Volume of iodide space....	litres	25	25
Thyroid weight.....	grams	20	60
Extrathyroidal organic iodine pool.....	litres	24	24
Iodine concentration in iodide pool.....	µg./litre	3.0	4.14
Concentration of organic iodine in thyroid.....	µg./kg.	400,000	91,700
Concentration of organic iodine in extrathyroidal organic pool.....	µg./litre	50	140
Thyroidal plasma clearance for iodide.....	ml./min.	16.2	100
Renal plasma clearance for iodide.....	ml./min.	33.3	33.3

*From Riggs, D.C.: Quantitative aspects of iodine metabolism in man, *Pharmacol. Rev.*, 4: 284, 1952.

importance, but can occasionally result in radiation reactions in these organs when large doses of I¹³¹ are administered (e.g. in treatment by thyroid ablation of angina pectoris, or in thyroid carcinoma).

HISTORY OF RADIOACTIVE IODINE

A brief quarter of a century ago, it was announced that radioactive isotopes could be produced artificially. Fermi, in 1934, first prepared a radioactive isotope of iodine (I¹²⁸).¹¹ However, at that time these events caused little stir amongst physicians. In 1938, Hertz *et al.*¹² introduced radioactive iodine as a diagnostic tool in thyroid studies, and subsequently similar studies were made by Hamilton and Soley.¹³ In 1942, the use of radioactive iodine (I¹³⁰) as therapy for hyperthyroidism was introduced by Hertz and Roberts,¹⁴ and Hamilton and Lawrence.¹⁵ At that time, radioactive isotopes were obtainable only from cyclotrons, usually at great cost, and frequently in such form as to require considerable chemical manipulation before they could be used.

The discovery and development of the chain-reacting pile, or nuclear reactor, changed this picture. It was not until 1946 that reactors were used to provide isotopes for non-military purposes. I¹³¹ subsequently became readily available. In the succeeding years, large numbers of institutions have come to utilize I¹³¹ in the study and therapy of thyroid disease, and wide experience has been gained and reported. For a more exhaustive treatment of the historical aspects of radioactive iodine, the reader is referred to the excellent monograph by Chapman and Maloof.¹

Rationale for the Use of Radioactive Iodine Therapy for Hyperthyroidism

The use of radioactive iodine in hyperthyroidism is based on two facts:¹

- 1. The thyroid gland has a natural avidity for collecting iodine.
- 2. Within the thyroid gland the radioactive iodine decays by emitting high energy beta rays which penetrate only a few millimetres into the tissue; both beta (β) and gamma (γ) rays are emitted by I¹³¹. Thus the dose delivered to each gram of thyroid by means of I¹³¹ is much greater than that which could be delivered by radiation from outside the body without causing harm to extra-thyroidal tissues.

I¹³¹ with a half-life of eight days is by far the most commonly used radioactive isotope of iodine; as noted, I¹³⁰ was utilized before 1946, and I¹³³ is at present occasionally employed.¹⁷ A table of some of the isotopes of iodine of medical interest has been taken from Werner,⁴ and herein reproduced for interest (Table II).

TABLE II.—IODINE ISOTOPES OF POSSIBLE INTEREST IN MEDICINE*

Isotope	Half-life	Radiation	Method of production
I ¹²⁴	4 days	β ⁺ , γ	cyclotron
I ¹²⁶	13 days	β ⁺ , β ⁻ , γ	cyclotron or pile
I ¹²⁷	stable	—	—
I ¹³⁰	12.6 hours	β ⁻ , γ	cyclotron
I ¹³¹	8 days	β ⁻ , γ	pile
I ¹³²	2-4 hours	β ⁻ , γ	pile
I ¹³³	22 hours	β ⁻ , γ	pile
I ¹³⁵	6-7 hours	β ⁻ , γ	pile

*From: Werner, S. C.: The thyroid, Harper & Brothers, New York, 1955.

A discussion of the possible biological hazards of I¹³¹ is elaborated in the section of this paper headed "Discussion".

PRESENT REVIEW

Selection of Patients

The present review includes 542 hyperthyroid patients who were treated by I¹³¹ in the Toronto General Hospital between December 1950 (when radioactive iodine was introduced by M.W.J. into this institution) and July 1958. It includes all public patients (whether inpatients or outpatients), as well as all private inpatients who were so treated during this period. It does not include private outpatients similarly treated by the authors, although the number of such patients is more than twice those actually included in the review.

In the first few years, only hyperthyroid patients over 40 years of age were selected for I¹³¹ therapy. In subsequent years the age limit was lowered, and it is our current practice to treat all hyperthyroid patients over 25 years of age with this isotope, with the exception of pregnant or lactating females. A few exceptional cases treated by I¹³¹ fell in the age group 18 to 25 years; these were persons who

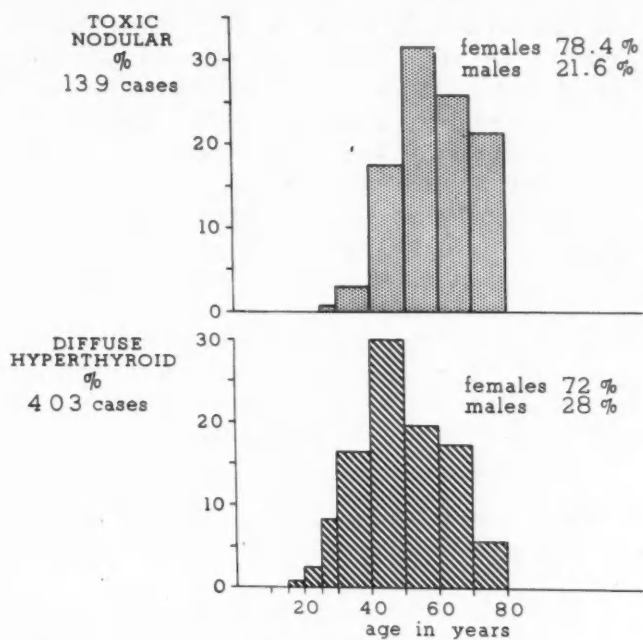


Fig. 1.—Age distribution in 542 hyperthyroid patients treated with I^{131} .

had complicating illnesses, or who had had previous thyroidectomy, or who had failed to experience remission on long-term antithyroid drug therapy coupled with refusal to undergo thyroidectomy.

We have not been concerned about the occurrence of thyroid malignancies in toxic nodular goitres and thus have treated all such patients with I^{131} , since the co-existence of thyroid cancer and hyperthyroid nodular goitres is very rare.¹⁰²

FOLLOW-UP OF PATIENTS

Patients given I^{131} therapy were, in general, followed up at 6- to 8-week intervals for six months, and then at variable intervals thereafter. For those patients who had not continued to attend the Endocrine Clinic at least annually, and had not been seen by us for at least one year, letters were sent requesting the patients to make a return visit; in lieu of a visit a letter from the patient or his doctor was requested regarding present clinical status. We have thus obtained at least a one-year follow-up in 85% of patients (Table III). In addition to clinical observation, various thyroid function tests were performed; however, the serum protein-bound iodine and 24-hour thyroid uptake of I^{131} were the major indices utilized. The serum protein-bound iodine assessment was performed by a modification of the method of Barker,¹⁸ in our laboratory the normal range is 3.5-6.5 $\mu\text{g. \%}$.¹⁹ The normal range for the 24-hour I^{131} thyroidal uptake in Toronto is 10 to 40%.

DOSAGE OF I^{131}

The method for estimating the dose of I^{131} for a given hyperthyroid patient varies widely from centre to centre. In some hospitals, the technique involves administration of repeated small doses of I^{131} (e.g. 2.0 mc.*) every few weeks until clinical remission is observed.²⁰ This form of therapy often permits the patient to remain hyperthyroid for excessively long periods. Further, since the efficacy of a single dose cannot be accurately assessed for

TABLE III.—LENGTH OF FOLLOW-UP

Time first treated	Less than 1 year	1-2 years	2-3 years	3-4 years	4-5 years	5-6 years	6-7 years	7-8 years	8-9 years	Total cases
July 1, 1950 - July 1, 1951	4	6	5	1	0	1	5	6	7	35
July 1, 1951 - July 1, 1952	14	27	10	9	5	5	18	18		106
July 1, 1952 - July 1, 1953	4	10	4	6	6	8	11			49
July 1, 1953 - July 1, 1954	10	23	10	4	11	18				76
July 1, 1954 - July 1, 1955	11	18	13	8	15					65
July 1, 1955 - July 1, 1956	12	27	20	16						75
July 1, 1956 - July 1, 1957	11	33	29							73
July 1, 1957 - July 1, 1958	21	42								63
	87	186	91	44	37	32	34	24	7	542

It is considered that I^{131} therapy is contra-indicated in the growth period, and during pregnancy or lactation.

The 542 patients considered in this review have been divided into two basic groups: those with diffuse hyperplastic goitres (Graves' disease), which includes 403 patients and those with toxic nodular goitres (139 patients). These two types of hyperthyroidism differ etiologically and clinically, as well as in their response to treatment. (This statement is admittedly controversial.)

The age and sex distribution is depicted in Fig. 1. It should be noted that the patients with toxic nodular goitres in this series are, in general, older than those with diffuse hyperplastic goitres. The usual female preponderance is noted.

at least eight weeks, it would seem that there might be a "pile-up" of doses before remission occurs; thus the incidence of hypothyroidism would not be reduced by such a regimen. However, results with this method have recently been reported by DeGowin *et al.*¹⁰⁷ which compare favourably with any other method of I^{131} administration.

In some other institutions, the "standard dose" method is employed²¹ in which standard initial doses in the order of 4 mc. I^{131} are given to all patients with toxic goitre. In those not responding to the initial dose, further similar doses are administered at 2- to 4-month intervals. However, it has been shown that the variation in sensitivity of the thyroid gland will greatly influence the response

*mc. = millicurie.

to single, standard 3 to 4 mc. doses. Radiation as low as 2690 rep* has produced hypothyroidism, while hyperthyroidism has persisted despite delivery of 10,000 rep to the gland.^{22, 23}

The more generally accepted form of therapy is the administration of a single (non-standardized) dose which is *calculated to control the disease*; it is then necessary to wait until the effect of the initial dose can be assessed before deciding on the need for further therapy. Despite the wide variation in thyroid sensitivity to radiation, some authors prefer to calculate the amount of radiation introduced into the gland by the dose of I¹³¹. This may be calculated (within wide limits) as follows:^{24, 25}

$$\begin{aligned} \text{Dose to thyroid in rads}^\dagger &= \frac{120 \times \text{effective half-life} \times \mu\text{c. I}^{131} \text{ in gland}}{\text{weight of gland (grams)}} \\ &\quad \text{or, assuming a half-life of 6 days:} \\ \text{Dose in rads} &= \frac{90 \times \mu\text{c. I}^{131} \text{ in gland}}{\text{weight of gland in grams}} \\ \text{Blomfield et al.}^{26} &\text{ use the following formula to estimate gland radiation:} \\ \text{Expected rads/mc.} &= \frac{820 \times 48\text{-hr. percentage uptake in preliminary tracer study}}{\text{estimated thyroid gland weight in grams}} \end{aligned}$$

These authors attempt to deliver a dose to the thyroid gland in the region of 7000 rads in the average uncomplicated case of thyrotoxicosis.

Although the use of the effective half-life of the tracer dose of I¹³¹ in calculation of the radiation delivered by the therapeutic dose has its adherents,^{23, 27} the correlation between the effective half-lives of the therapeutic and tracer doses has been shown to be only fair;^{28, 30} thus this consideration is generally disregarded in dosage estimations. It may well be, however, that some instances of retreatment are due to an unusually short effective half-life, with consequent reduced glandular irradiation.

Because of the difficulties involved in estimating thyroid gland size clinically, and because of the unpredictable response, most workers (including the authors) disregard the radiation calculation and administer the initial dose of I¹³¹ based mainly on microcuries (μc.) retained per gram of estimated thyroid tissue. Even the method by which this "guesstimate" is calculated varies considerably from clinic to clinic. In our clinic an average dose of 120 microcuries of I¹³¹ per gram of estimated thyroid weight in diffuse hyperplastic goitres seems to produce the desired beneficial effects in most instances (see below); this dosage is based on a 24-hour I¹³¹ thyroid uptake of 50%. If the uptake is higher, the dose is decreased.

Several other factors have a bearing on the assessment of the initial dosage. These include the

duration and severity of the illness, consistency and geometry of the thyroid gland, and previous thyroidectomy or antithyroid medications.

It is a curious observation that the good therapeutic results from clinic to clinic are not too disparate, despite the wide differences in methods of estimating dosage, and the crude and arbitrary manner in which dosages are decided.

It is of great importance to note that most of the foregoing remarks regarding dosage estimation pertain to those hyperthyroid patients with diffuse hyperplastic goitres. In the toxic nodular group, after an initial trial and error period (1950-52) in which comparatively small and therefore repeated

doses were utilized, we have come to administer much larger doses (despite considerations of gland size), usually in the order of 20 to 45 millicuries (mc.); these doses are somewhat smaller than those suggested for toxic nodular goitres by the Cleveland Clinic group.³¹ On the other hand, Eller *et al.*¹⁰⁵ have treated toxic nodular goitres with the same dosage estimations as those applied to patients with diffuse goitres and have achieved very satisfactory results.

The initial dose of I¹³¹ used for the authors' patients is recorded in Fig. 2. It can be noted from this figure that most patients with diffuse hyperthyroidism received initial doses varying between 3 and 10 mc.; actually 21.9% of these patients received between 4 and 5 mc. I¹³¹ as their initial dose. On the other hand, the majority of patients in the toxic nodular group received over 10, and usually over 15 mc. It should be emphasized that Fig. 2 contains dosage results from the initial "trial and error" period, as well as more recent results; the small doses below 10 mc., and most of the 10-15 mc. doses, shown in the toxic nodular group, are from the early period. Some of the very small doses in the diffuse group are also from this early period, and are not wholly representative of our present methods of estimation.

Although the chart is not entirely representative (as a result of the early misleading data), it presents a reasonable picture of our dosage estimation.

NEED FOR RE-TREATMENT WITH I¹³¹

Generally there are no clinical changes (either in symptoms or signs) for approximately three to four weeks after the dose has been administered.

*The "rep" (roentgen equivalent physical) is defined as that quantity of any ionizing radiation from which the energy imparted to soft tissue by the ionizing particles is 93 ergs per gram of tissue.

†The "rad" is a unit measure of energy imparted by ionizing particles per unit mass of irradiated matter. One rad equals 100 ergs per gram of tissue radiated.

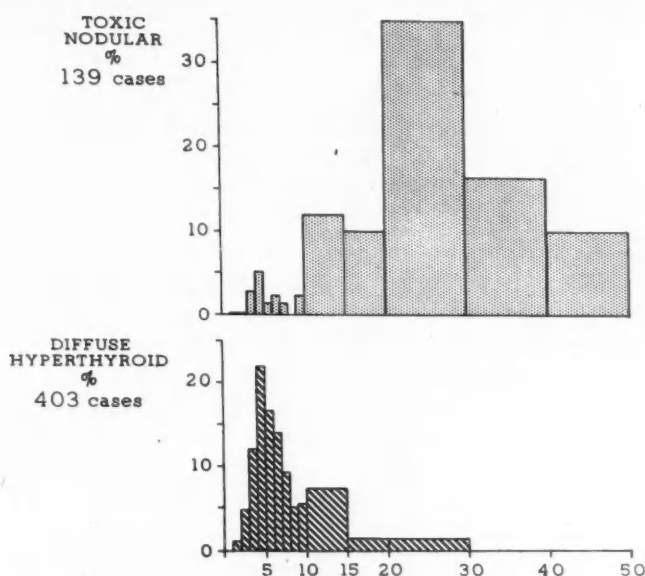


Fig. 2.—Initial dose in millicuries of I¹³¹.

At this time there is usually a gradual improvement in symptomatology, which progresses thereafter for several weeks. In two to four months, most patients have reached a euthyroid state (Fig. 6), and some of these will develop hypothyroidism.

In patients who remain hyperthyroid after their initial dose, further doses are subsequently administered. If there is no improvement whatever, or actual clinical deterioration at the eight-week period, a second dose may then be administered; however, second doses are rarely administered before three months have elapsed after the initial dose. At the two to three month interval, re-treatment doses should be reserved for those who have shown very little or no improvement, and should be withheld from those who (while still hyperthyroid) are continuing to improve.

For the latter group it may be found that gradual slow improvement may continue for several months, and may lead to eventual complete recovery without a second dose; this may occur many months after the usual time of recovery. It is a good clinical

rule to withhold further therapy if the patient is continuing to gain weight. However, once a plateau of no further recovery is reached, a second dose should be administered.

Some patients will become euthyroid after their I¹³¹ therapy, then rebound back to hyperthyroidism; these patients usually require another dose. A few of these will recover spontaneously even if another dose is *not* administered. Late recurrences (after remaining euthyroid for six to nine months) were not observed in our series.

From Fig. 3 it can be seen that 72% of those in our "diffuse" group were cured by a single dose, 20.2% by two doses and 7% by three doses, and 1.4% required more than three doses. Some of those requiring three or more doses were treated with successive small doses (2 to 4 mc.) in our period of inexperience; others were in the "resistant" group, in which final large doses (20 to 40 mc.) were necessary for cure. We had no instances in which I¹³¹ resistance was sufficiently pronounced to prevent final recovery, and it was never necessary to resort to surgical extirpation of the gland.

In the "toxic nodular" group, 79% required only one dose for recovery, while 11.5% received two doses, and 7.2% three doses; 2.1% received more than three doses. It should be noted once again that the majority of patients receiving two doses or more in this group were so treated between 1950 and 1952, before it was appreciated that toxic nodular goitres required much larger doses of radioactive iodine for good results. Thereafter, *no patient* in this group required more than two doses for cure, and even a second dose became a rare event. Indeed, the treatment of toxic nodular goitres with I¹³¹ in our hands is now carried out with more success than is the treatment of diffuse hyperthyroidism. Utilizing the much larger initial doses, recovery without a second dose is much more consistent, and hypothyroidism (see below) is less common than in those with diffuse hyperthyroidism. This might be anticipated from the functional studies of toxic nodular goitres in which hyperplastic areas in the gland are surrounded by resting areas in which there is little avidity for iodine; the possibly autonomous hyperfunctioning nodule causes an elevation of blood thyroxine which may suppress pituitary TSH; at any rate, the surrounding thyroid parenchyma appears involuted. The therapeutic I¹³¹ destroys the hyperfunctioning area(s), after which the resting areas recover their normal function. By experience, it was found that calculating the dose for toxic nodular goitres on the same basis as that used for diffuse hyperplastic goitres necessitated re-treatment in most cases; thus, the larger doses (mentioned above) came to be utilized.

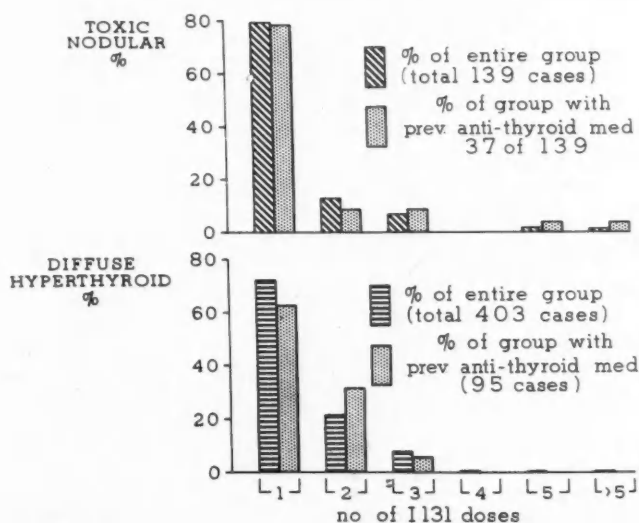


Fig. 3.—Number of doses of I¹³¹ in entire group (542 patients) and in those previously given antithyroid drugs.

ESTIMATION OF SUBSEQUENT DOSES

If recovery does not follow the initial dose of I¹³¹, subsequent doses must be estimated and ad-

ministered, using the foregoing criteria for re-treatment.

If at the 8- to 12-week interval after the initial dose there was no improvement whatever, or if there was actual clinical deterioration, a dose approximately double the initial dose was administered. If the patient responded well initially and then rebounded to a hyperthyroid state, a dose only slightly larger than the original dose was utilized. If there was some mild improvement after the first dose, with no further recovery, a dose roughly equivalent to the first dose was given. On the other hand, if there was considerable improvement which just fell short of complete recovery (and the patient was not continuing to improve), a dose smaller than the original one was administered. Similar practices were employed if still further treatments became necessary.

FACTORS ASSOCIATED WITH NECESSITY FOR RE-TREATMENT

Patients receiving more than one dose were studied to determine possible factors which may have led to the need for re-treatment. The small doses utilized in the "nodular" group in our early experience have already been mentioned as a major factor leading to re-treatment of that group. Age, sex, severity of illness, thyroid indices, or previous thyroidectomy bore no relation to re-treatment. In the "diffuse" group, the size of the initial dosage did not correlate well with the need for re-treatment; in these patients only estimated gland size appears to correlate with the necessity for further radiation; i.e. the larger the gland size the greater the number of doses necessary for cure (Fig. 4). In this series, scanning was not frequently utilized to check on gland size; estimation of the size of the gland was made on the basis of palpation only, admittedly an inaccurate method. By comparing scanning results with estimation of gland size by palpation, Blomfield *et al.*²⁶ have shown that palpation leads to overestimation of the size of smaller glands and underestimation of that of larger glands. These authors, comparing their estimates of gland size with their clinical results, found that the percentage of patients still hyperthyroid after the first treatment rose with increasing gland mass, and the proportion who became hypothyroid fell.

USE OF ANTITHYROID DRUGS IN ASSOCIATION WITH RADIOACTIVE IODINE THERAPY

It is our current practice to employ antithyroid drugs in preparation for I^{131} therapy only in those patients who are severely ill with hyperthyroidism, or in those with associated cardiovascular disease. This form of therapy depletes the gland of colloid (if there is any stored colloid), thus preventing a possible post- I^{131} exacerbation of hyperthyroidism due to the radiation thyroiditis. In previous years this therapy was not always utilized in patients with cardiovascular disease; this may have been

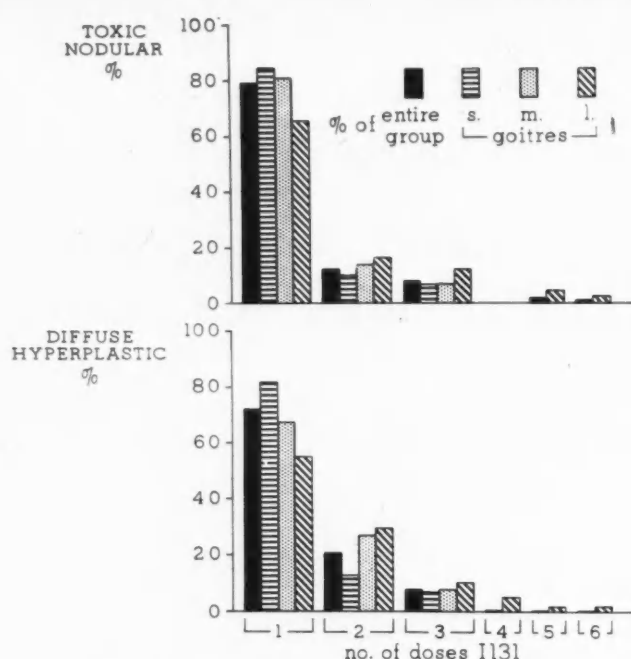


Fig. 4.—Number of doses of I^{131} correlated with size of goitre. s = small, m = medium, l = large.

a factor in some of the cardiovascular deaths (see below) which followed shortly after I^{131} therapy, although none of these deaths could be definitely related to treatment.

Antithyroid drugs were administered before I^{131} therapy in 95 (23.6%) of the "diffuse" hyperthyroid patients, and in 37 (26.5%) of the "toxic nodular" group. In most instances the drug was given for several weeks, and was discontinued in the week prior to the I^{131} dose.

As suggested by Crooks *et al.*,⁹² the preliminary administration of these drugs seemed to be associated with a slight decrease in radiosensitivity

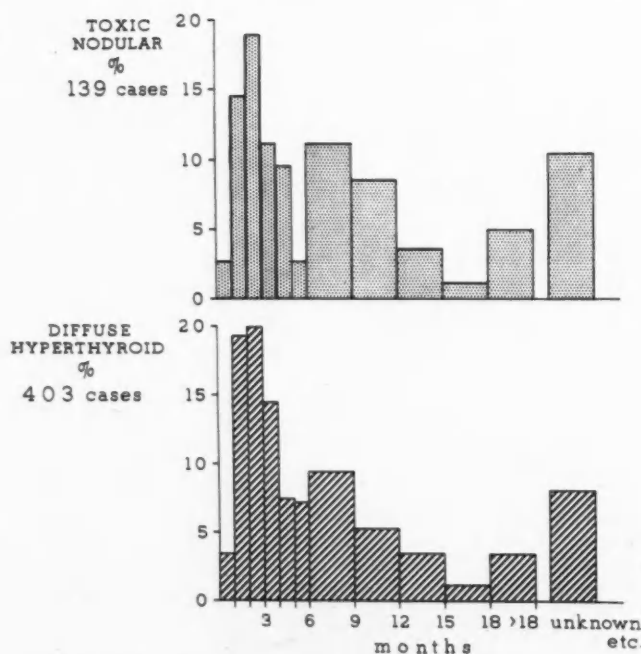


Fig. 5.—Time required to attain euthyroidism following initial dose of I^{131} . It should be noted that the "unknown" group includes patients whose date of recovery could not be adequately assessed, as well as patients who failed to return for follow-up and patients who died while still hyperthyroid.

in the "diffuse" group, as judged by the mild increase in the number requiring re-treatment (Fig. 3); but there was no increase or decrease in the incidence of post- I^{131} hypothyroidism in those pre-treated with antithyroid drugs.

It has not been our practice to administer antithyroid drugs after I^{131} therapy (although for various reasons this was done in 15 cases [2.8%]). In the latter small group of patients, the tablets were not started until at least one week after the dose of radioiodine, so that the lack of re-entry of I^{131} (from degraded organically bound I^{131}) would not be an important factor in decreasing I^{131} effectiveness; in six of these patients it was not started until it was clear that the previous dose of I^{131} was not going to produce a remission. There were too few remaining cases to assess accurately the role of such therapy.

Generally, it has not been considered necessary to use antithyroid drugs in the post-treatment period. It has also been felt that such therapy might interfere with the assessment of the efficiency of the I^{131} dose. However, Cassidy and Astwood³² have found that the post- I^{131} administration of antithyroid drugs did not diminish effectiveness of I^{131} therapy, as judged by the need for repeated doses, and actually seemed to be associated with a reduction in the subsequent myxedema rate.

(To be continued)

VERRUCOUS CARCINOMA OF THE BUCCAL MUCOSA IN TOBACCO-CHEWERS*

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SQUAMOUS CELL carcinoma is the most common malignant neoplasm affecting the oral mucosa. Such tumours may present considerable histological variation, but the majority are only moderately well differentiated.¹ They are frequently preceded by leukoplakia. Syphilis, dental irritation, smoking and the Plummer-Vinson syndrome are recognized as factors which probably predispose to oral cancer. More specifically, in carcinomas of the buccal mucosa the chewing of betel nuts, as practised in many countries of the Far East, and of tobacco including snuffs is considered to be an important predisposing factor.

In 1948 Ackerman² defined a separate variety of squamous carcinoma of the buccal mucosa which is characterized by a predominantly exophytic

RESPONSE TO I^{131} THERAPY

The duration of time required for remission of hyperthyroidism after radioactive iodine therapy varies considerably, although most patients reached a euthyroid state within five months after the first treatment (see Fig. 5). It is readily apparent that those persons requiring more than one dose will generally take longer to reach remission than those requiring only a single dose. Included in the multiple-dose group were some " I^{131} -resistant" patients, who required total doses much larger than those anticipated by our usual criteria for dosage estimation. We found no patients who could not be cured finally with I^{131} ; four patients in the "diffuse" group were given total dosages greater than 40 mc., the largest total dose being 51 mc., while one elderly patient with a toxic nodular goitre received a total of 124 mc. before recovery was attained. It was not found necessary to resort to thyroidectomy in any patient given radioactive iodine, contrary to the experience of Bartels.³³ Some patients cured with a single dose nevertheless took many months (of gradual improvement) before their disease subsided. Another factor which sometimes prolonged therapy was the inconstant attendance at follow-up clinics of a small number of patients; some of these would have been re-treated much earlier, had they appeared on time.

growth. In the great majority of patients with this verrucous type of squamous carcinoma a history of tobacco-chewing could be obtained.

The present report deals with four such cases of verrucous carcinoma of the buccal mucosa which were encountered in old men with a longstanding history of tobacco-chewing. In view of the fact that this variety of oral cancer carries a much better prognosis than the more usual squamous cell carcinomas of the mouth² and since a 1- to 7-year follow-up is available in three of the four cases, it would seem to be justified to draw further attention to this lesion.

CASE 1.—This 78-year-old man was first seen at the Nova Scotia Tumour Clinic on July 18, 1956. At this time he had papillomatous growths on the left buccal mucosa along the inferior buccogingival sulcus and extensive leukoplakia on the hard palate. No enlargement of regional lymph nodes was noted. The clinical diagnosis was carcinoma. Biopsies were taken and reported as verrucous carcinoma or tobacco papillomatosis of the mouth. Two cauliflower-like growths were excised from the left buccal mucosa, and a third one, also on the left side, was cauterized. The patient stated that he used to smoke but he had given this up and had been chewing tobacco for about ten years. In October 1956 there was a recurrence of the papilloma-

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Fig. 1.—Case 1. Low-power view of first biopsy demonstrating characteristic verrucous nature of lesion. Hematoxylin and eosin.

tous growth over the left alveolar margin and over the centre of the left cheek. These were excised and again reported as verrucous papilloma. In July 1957 there was no evidence of recurrence. There was some leukoplakia present which was cauterized. In January 1960 a squamous cell carcinoma was removed from the upper lip and a basal cell carcinoma from the left eyebrow. There was no evidence of recurrence of the verrucous papilloma.

Microscopically, on both occasions, the tissue was essentially a squamous papilloma (Fig. 1). There was marked acanthosis and slight parakeratosis of the squamous epithelium especially in the depth of the crypts (Fig. 2). The squamous epithelium was well differentiated and showed only little loss of polarity and minimal cellular atypia. The underlying fibrous connective tissue was infiltrated mainly by lymphocytes, plasma cells and some polymorphonuclear leukocytes. The squamous epithelium was slightly infiltrated by these inflammatory cells (Fig. 3). A few apparently isolated nests of well-differentiated squamous epithelium were present in the base of the papilloma, but there was no actual invasion.

CASE 2.—This 76-year-old man was given a course of x-ray treatment first in April 1948 and again in November 1949, for a lesion of the lower lip diagnosed clinically as carcinoma. It had apparently never been



Fig. 2.—Case 1. Photomicrograph of Fig. 1 showing marked acanthosis and parakeratosis of squamous epithelium. Hematoxylin and eosin.

biopsied. He was first seen in the Nova Scotia Tumour Clinic at the Victoria General Hospital in September 1953. At this time the lower lip showed some scarring and suspicion of leukoplakia. There were small warty growths in the right inferior buccogingival sulcus. The leukoplakia was cauterized. The papillomas were biopsied and diagnosed on histological examination as squamous papilloma.

In May 1954 the right buccal mucosa showed multiple papillomatous lesions. These were biopsied and reported as epidermoid carcinoma, grade I. The treatment consisted of insertion of radium needles into the buccal mucosa. In July 1954, the patient returned and there were again dense papillomatous areas over the anterior portion of the right buccal mucosa. Cauterization was carried out. In December 1954 the right buccal mucosa appeared to be quite healthy

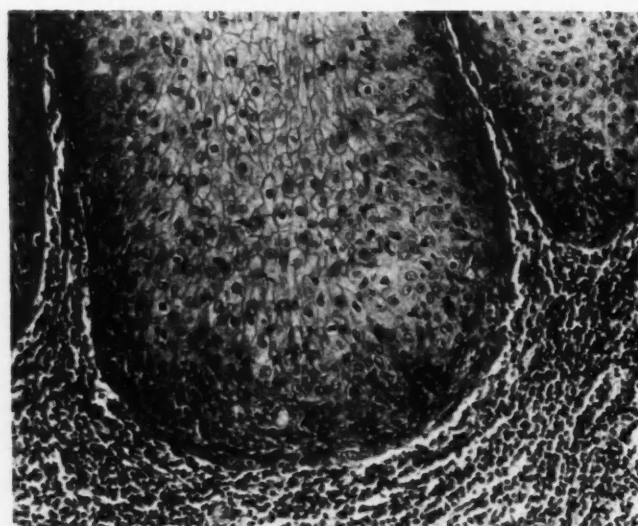
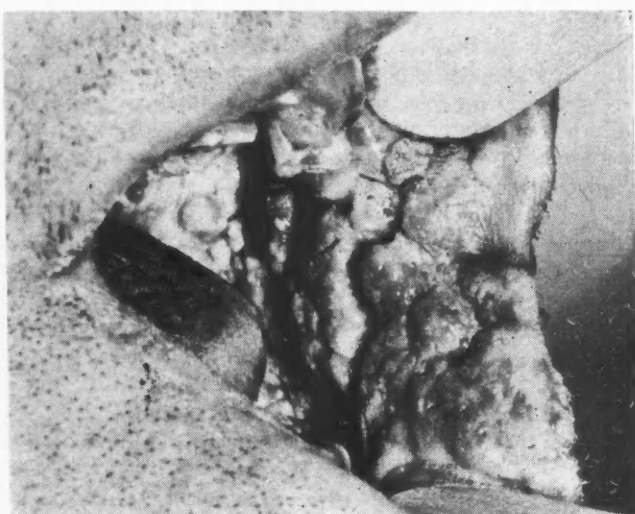


Fig. 3.—Case 1. Photomicrograph revealing well-differentiated appearance of squamous epithelium and nature of inflammatory reaction. Hematoxylin and eosin.

except for an area of induration about one inch in diameter near the angle of the mouth. In the centre of the indurated area there was a small ulcer. A biopsy showed chronic inflammation only. In April 1955 there was some scarring of the buccal mucosa but there was no evidence of any recurrence. In March of 1956, the right buccal mucosa was rather irregular and there was a circumscribed area, about one inch in diameter, of proliferative growth, again near the angle of the mouth. There was no enlargement of regional lymph nodes. In August 1956, the right buccal mucosa appeared to be irregular and highly suspicious of recurrent tumour. A biopsy was taken and again showed a papillomatous lesion. In February 1958 there was gross papillomatosis of the buccal surface of the right cheek and along the lower lip. The patient was advised to enter hospital at that time but did not do so. No further treatment was carried out.

In April 1960 the patient presented with extensive papillomatous lesions involving almost the entire right buccal mucosa and extending on to the lip on the right. A small lesion was also present on the left lower lip. These felt rather soft (Figs. 4 and 5). Regional lymph nodes were not enlarged. At this time biopsies were taken and the lesion was reported as verrucous papilloma. Treatment consisted of removal of these under general anesthesia and cauterization of the base. It



Figs. 4 and 5.—Case 2. Papillomatous lesion on right buccal mucosa extending on to the lip.

Figs. 6 and 7.—Case 3. Fungating, ulcerating lesion on left buccal mucosa extending on to hard palate.

was noted at the time of operation that many of the lesions could be peeled off. This patient gives a history of chewing tobacco and holding the cud, particularly on the right side of the mouth, ever since he was 15 years of age.

Review of the first biopsy of 1953 showed a characteristic papillary tumour, the appearances of which were almost identical to those presented by the most recent biopsy taken in April 1960. Similarly, the biopsies of May 1954, diagnosed as epidermoid carcinoma, grade I, and of August 1956, were typical of a verrucous carcinoma. The remaining two biopsies included areas of inflammation and of leukoplakia only. The most recent biopsy of April 1960 was reported as a low-grade papillary squamous carcinoma of the buccal mucosa. There were three specimens and they all had a papillary structure. The squamous epithelium showed keratinization and acanthosis and was supported by thin vascular stalks of fibrous tissue. Thick rete pegs extended into the underlying fibrous connective tissue which was infiltrated by plasma cells and lymphocytes. The squamous epithelium in general was well differentiated, but there were areas of cellular atypia and of dyskeratosis in association with the inflammatory cell infiltrates. At the base of the lesions isolated nests of squamous cells were present, but there was insufficient underlying tissue to assess deep invasion.

CASE 3.—This 71-year-old man was first seen in March 1960, at which time he had a fungating and ulcerating lesion covering the whole of the buccal surface of the left cheek as far back as the tonsillar fossa and involving the lower lip (Fig. 6). It also extended up on to the hard palate (Fig. 7). He stated that this lesion had been present for at least six years and was gradually increasing in size. The regional lymph nodes were not palpable. The patient gives a history of chewing tobacco since the age of 16 years, and of holding the cud of tobacco on the left side of the mouth. He does not smoke. The clinical impression was that of a carcinoma. Biopsies were taken from three different areas and reported as verrucous papilloma. The lesion was observed for a period of one month, during which time the patient did not chew tobacco and observed strict oral hygiene. As a result the growth appeared to decrease in size. Subsequently in April 1960 the lesion was removed. It is noted again that much of this lesion could be peeled off. Areas were coagulated where bleeding was present.

Microscopically, all three tissue fragments presented a similar appearance. They were verrucous and the squamous epithelium was greatly thickened and cornified on the surface. Plump rete pegs of well-differentiated squamous epithelium extended deeply into the underlying fibrous connective tissue, which was densely infiltrated with lymphocytes and plasma cells. There was no evidence of deep invasion.

CASE 4.—This 83-year-old man first came to the Nova Scotia Tumour Clinic on September 26, 1956. At this time he had an extensive verrucous lesion of the right buccal mucosa, extending from the superior to the inferior buccogingival sulcus. It extended from the corner of the mouth as far back as the tonsillar fossa. The clinical diagnosis once again was squamous carcinoma. There was no evidence of regional lymph node enlargement. He stated that this lesion had been present for at least two months. He had smoked a pipe until two years previously, but had "always" chewed tobacco. Biopsy of this lesion was reported as verrucous carcinoma of the buccal mucosa. He was treated by a course of 15 treatments of 3000 r from a 250 KV machine, and was followed up for a period of one year only. At that time there was no evidence of recurrence.

Microscopically, the tissue fragments were composed mainly of squamous epithelium with little underlying connective tissue. The epithelium showed papillomatosis, acanthosis and surface keratinization. The subepithelial connective tissue was heavily infiltrated by lymphocytes and plasma cells. Isolated nests of squamous epithelium which showed considerable cellular atypia and dyskeratosis were present over the deep aspect of the lesion, suggesting the presence of invasion.

DISCUSSION

Among other chronic irritants, tobacco is believed to be an important predisposing factor in the development of oral cancer. Although the heat generated by smoking and the end-products of combustion of tobacco are considered to be sources of irritation, there is strong evidence that tobacco, when chewed, also acts as an irritant.³ It is also probable that the carcinogenic effect of the betel chew is due to tobacco, which is one of its ingredients.

In 1941, Friedell and Rosenthal⁴ reported eight cases of squamous cell carcinoma of the buccal mucosa and of the alveolar ridge. The patients were all men over 60 years of age, and gave a history of tobacco-chewing. The presence on clinical examination of papillary lesions was found to be almost pathognomonic.

In 1948, Ackerman² reported 31 cases of verrucous carcinoma of the oral cavity. He clearly defined the lesion and suggested that this type of tumour should be separated from the other types of squamous carcinoma of the mouth because of its slow growth, its well-differentiated appearance, its local invasiveness with only extremely rare local metastasis and complete absence of distant metastasis. A history of tobacco-chewing was obtained in a high percentage of the cases.

There can be little doubt that the four cases presented here fall into the group of verrucous carcinoma. The lesions were present in old men all of whom gave a history of tobacco-chewing of many years' duration. The clinical and pathological findings of the verrucous lesions in association with areas of leukoplakia were quite characteristic. Clinically, in all four cases the lesions were ex-

tremely extensive and strongly suggested the presence of massive carcinomatous infiltration, yet none showed clinical evidence of lymphadenopathy or of distant metastasis. With regard to the question of regional lymphadenopathy, however, it must be remembered that oral carcinomas are frequently accompanied by considerable secondary inflammation which may lead to reactive enlargement of the lymph nodes and thus suggest the presence of metastasis in these nodes. Similarly, the primary lesion in the mouth itself may in part derive its malignant clinical appearance from secondary inflammation. This latter fact was borne out in Case 3 where a reduction in the size of the lesion was obtained after a short but intensive course of oral hygiene.

Although, according to the cases reported in the literature, local invasion by these tumours is not uncommon, in three cases of the present series the lesion appeared to be confined to the surface. In Cases 2 and 3 it was even possible to peel off much of the lesion at operation. In Case 2, although it had recurred, the lesion had not changed significantly over a period of seven years. The patient of Case 3 has been under clinical observation for only a short period of time (a total of five months) and no definite conclusions can be drawn as to the ultimate behaviour of this tumour. It can, however, be argued that if we were dealing with the usual type of oral cancer, such an extensive lesion of six years' duration would almost invariably be associated with at least regional lymph node involvement.

Only in Case 4 was there a sufficient degree of cellular pleomorphism of the squamous epithelium and evidence of infiltration by the tumour of the underlying connective tissue to justify the diagnosis of carcinoma on histological grounds. This patient unfortunately could be followed up for only one year. It is remarkable that the remaining three patients have so far not revealed any evidence of invasion although the lesions had recurred once in Case 1 and twice in Case 2 over periods of four and seven years respectively and had remained entirely untreated for a period of six years in Case 3. On histological grounds the lesions might be more correctly termed verrucous papillomas. Experience of others who have been able to study larger numbers of cases, however, shows that local invasion does occur. Furthermore, owing to the complex nature of the histological changes at the deep aspects of the lesions and the frequent presence of fraying or of disappearance of the basal layer of the squamous epithelium in association with a heavy inflammatory reaction and varying degrees of cellular atypia, invasion cannot always be easily excluded. In practice therefore, when taking into account the overall available experience, lesions of this type are justifiably classified as low-grade carcinomas.

The present group of cases emphasizes the concept that verrucous lesions of the buccal mucosa of tobacco-chewers should be regarded as

an entity which deserves to be separated from the more usual type of oral cancer on account of its relatively benign behaviour. Local excision of the oral tumour is considered to be the treatment of choice in such cases. It goes without saying that the habit of tobacco-chewing should be discontinued.

SUMMARY

Four cases of verrucous carcinoma of the buccal mucosa of tobacco-chewers are reported. The longest follow-up period was seven years. Although the lesions

recurred locally in two of the four cases, they were characterized by the absence of local or distant spread. The need for awareness of this entity and for its separation from the usual type of squamous carcinoma of the mouth is emphasized.

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GRISEOFULVIN TREATMENT OF SUPERFICIAL MYCOSES (INCLUDING 7 CASES OF FAVUS)*

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OUR PRELIMINARY report,¹ published in November 1959, described the treatment of 11 patients with superficial mycoses by oral griseofulvin. The present paper will discuss the results of treatment by this antibiotic in 47 patients, including 7 patients with favus.

Several hundred clinical observations have been reported in the recent medical literature. They all point out the beneficial action of griseofulvin and emphasize its low toxicity. Most of these observations were presented at the International Symposium on Griseofulvin² held in October 1959 at Miami, Florida, and attended by dermatologists, microbiologists and pharmacologists from all parts of the world. The subjects discussed included laboratory investigations, experiments on animals and human clinical studies. Among the important findings reported at this Symposium are:

1. *In vitro* resistance to griseofulvin has been demonstrated by *Trichophyton rubrum* and *Microsporum canis*. However, such a phenomenon has not been observed in man or animals.
2. Griseofulvin has no harmful effect on spermatogenesis, as demonstrated by numerous sperm counts and testicular biopsies. Only mild reactions to the drug have been reported among hundreds of patients. Laboratory tests showed no alteration in renal, hepatic and hematopoietic functions.
3. Reinfections and recurrences have been reported, but it must be kept in mind that there is often clinical healing of the lesions while the cultures are still positive. In such cases, the disease will reappear if the treatment is stopped.

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Griseofulvin administration with topical medication and hair clipping seems to shorten the duration of the treatment, and to eliminate the risk of reinfection in the treatment of tinea capitis.

4. One case of favus was reported and the result of treatment seemed favourable.

5. Most of the clinical studies were additional proof of the value of griseofulvin, and were carried out to find out the duration of treatment needed for the superficial mycoses and the ideal daily dosage.

Aside from the symposium Degos and Lefort reported the successful treatment of 34 cases of tinea capitis with griseofulvin. These authors described 23 cures, including 5 in patients with favus.

Kirk and Ajello⁴ have treated 81 patients suffering from tinea capitis. Seventy of these infections were caused by *Microsporum audouinii*. Daily dosage ranged from 3.1 mg. to 25 mg. per lb. of body weight. The optimal dose seemed to be 10 mg. per lb. Infections of a year or more responded better to griseofulvin than acute infections. The same authors recommended that the treatment be continued until two negative cultures are obtained; otherwise, reinfection could be expected. In a series of 10 patients, Wood's lamp showed fluorescent hair up to 25 days after the beginning of treatment. In two other cases, the fluorescence persisted for 42 days. In ten cases, cultures were negative after 70 days. In some, positive cultures were obtained after 95 days. These authors have also reported two cases of angioneurotic edema in patients being treated by griseofulvin.

Robinson *et al.*⁵ reported their results in 124 cases: Tinea capitis was cured in 5 weeks; tinea cruris healed in 4 to 8 weeks, tinea corporis in 4 to 9 weeks, and tinea pedis in 6 to 9 weeks or more. As to onychomycoses, 24 patients were still being treated after 11 weeks because the cultures were still positive, although most of these patients were considered clinically cured.

In Canada, Stewart *et al.*⁶ reported good results in six patients out of seven.

CLINICAL MATERIAL

Forty-seven patients with various superficial mycoses were treated by griseofulvin. Of this number, 28 had tinea capitis, 15 had tinea cruris, pedis or corporis, and 4 had onychomycosis (Table I).

TABLE I.—PATIENTS TREATED BY GRISEOFULVIN

Superficial mycoses	Etiological agent	Number
Tinea capitis	<i>M. canis</i>	19
	<i>M. audouini</i>	2
	<i>T. schönleini</i>	7
Tinea cruris pedis corporis	<i>E. floccosum</i> (2)	4
	<i>T. rubrum</i> (2)	3
	<i>T. mentagrophytes</i> (4)	8
	<i>M. canis</i> (2)	
Onychomycosis	<i>T. rubrum</i>	2
	<i>T. schönleini</i>	1
	Not isolated	1
Total number.....		47

Among the cases of tinea capitis, *M. canis* was responsible in 19, and *M. audouini* in 2. The seven cases of favus were caused by *T. schönleini*.

Fifteen patients were afflicted with dermatomycoses: 4 tinea cruris, 3 tinea pedis and 8 tinea corporis. Of these patients, the fungus was identified in 10: *E. floccosum* in 2 cases of tinea cruris, *T. rubrum* in 2 cases of tinea pedis, and *T. mentagrophytes* in 4 cases and *M. canis* in 2 cases of tinea corporis.

From the four patients with onychomycosis, *T. rubrum* was isolated in 2 and *T. schönleini* in 1. Repeated trials to identify the fungus in the other case were unsuccessful.

GRISEOFULVIN AND FAVUS

Seven patients with favus were treated by griseofulvin. Their ages were between 5 and 34 years. The infection had lasted from 2 to 30 years. All patients showed scarring alopecia to a certain degree, while two were affected more severely.

In five, the lesions were classical, showing sulphur yellow masses of varying size with central depression.

Before treatment, mycological examinations were made in all cases and yielded cultures of *T. schönleini*. Other cultures and examinations under a Wood's lamp were carried out every two to three weeks. One patient (Case 3) refused to co-operate and control became impossible.

Patients received 1 g. of griseofulvin per day, without topical treatment. They were instructed to cut their hair very short or, better, to shave it after three weeks of treatment, and to wash it twice a week. Three women patients partially neglected to take such care.

After three weeks of treatment, marked clinical improvement was noticed in all patients. The crusts were much less numerous and thinner. The proximal portion of hair was normal, and negative on Wood's lamp examination.

Normal regrowth of hair was more pronounced as the griseofulvin was continued. In two patients, it was interesting to observe that a few hairs showed fluorescence even in their proximal portion. It seemed that the antibiotic did not penetrate as rapidly in these hair follicles.

Six patients had no fluorescence after 7 to 12 weeks.

TABLE II.—GRISEOFULVIN AND FAVUS

Case	Age	Sex	Duration of disease (years)	Organism	Daily dose	Duration of treatment (weeks)	Results
1	27	F	22	<i>T. schönleini</i>	1.0 g. (8 w.) 0.5 g. (8½ w.)	16½	No fluorescence after 11 weeks. Negative culture after 12 weeks. Cured.
2	34	F	30	<i>T. schönleini</i>	1.0 g.	10	Clinical and mycological cure after ten weeks.
3	21	F	20	<i>T. schönleini</i>	1.0 g.	4 treatment continued	Marked clinical improvement after four weeks.
4	13	F	6	<i>T. schönleini</i>	1.0 g. (8 w.) 0.5 g. (4 w.)	12 retreatment	No fluorescence after seven weeks. Culture negative after eleven weeks. Cured. Reinfection two months later.
5	8	M	6	<i>T. schönleini</i>	1.0 g. (6 w.) 0.5 g. (7½ w.)	13½ treatment continued	No fluorescence, but culture positive after eleven weeks. Clinical cure.
6	5	M	2	<i>T. schönleini</i>	1.0 g. (3 w.) 0.5 g. (4½ w.)	7½ treatment continued	No fluorescence, but positive culture after eight weeks. Marked clinical improvement.
7	16	M	13	<i>T. schönleini</i>	1 g.	5 treatment continued	No fluorescence, but positive culture after five weeks. Clinical cure.

TABLE III.—TINEA CAPITIS AND GRISEOFULVIN

Organism	Number of patients	Age (years)	Duration of disease (wks.)	Daily dose	Duration of treatment (weeks)	Results
<i>M. audouini</i>	2	2½ 4½	4	0.5 g.	9	Clinical and mycological cure.
<i>M. canis</i>	2	2 4	6	0.25 g.	6	Clinical and mycological cure. Recurrence in one patient one month later.
<i>M. canis</i>	4	4 to 12	4 to 6	0.5 g.	7 to 10	Clinical and mycological cure in three. Clinical cure only in one.
<i>M. canis</i>	6	4½ to 13	4 to 8	1 g.	5 to 12	Clinical cure.
<i>M. canis</i>	5	3 to 7	4 to 20	0.5 g.	2 to 8	Marked clinical improvement. Fluorescence diminished in three. No fluorescence in two.
<i>M. canis</i>	2	8 months 1 year	4	0.25 g.	2	No improvement. Treatment continued.

RESULTS

Seven patients were considered clinically cured in 5 weeks. Five others obtained a clinical cure in 8 to 12 weeks. Cultures were negative in three patients after 11 and 12 weeks.

One patient (Table IV), regarded as cured clinically and mycologically, developed new lesions after two months. This seems to be an instance of reinfection, as a member of her family had untreated favus.

These seven patients belong to the same family. It has been possible to follow 22 cases of favus through four generations. It is very likely that their number was greater, because not all members of the family were seen.

	Members known	Cases of favus
First generation.....	—	1
Second ".....	13	7
Third ".....	19	7
Fourth ".....	20	7
		22

TINEA CAPITIS AND GRISEOFULVIN (TABLE III)

Twenty-one children (from 8 months to 12 years of age) received from 250 mg. to 1 g. of griseofulvin per day. In all instances, the diagnosis was

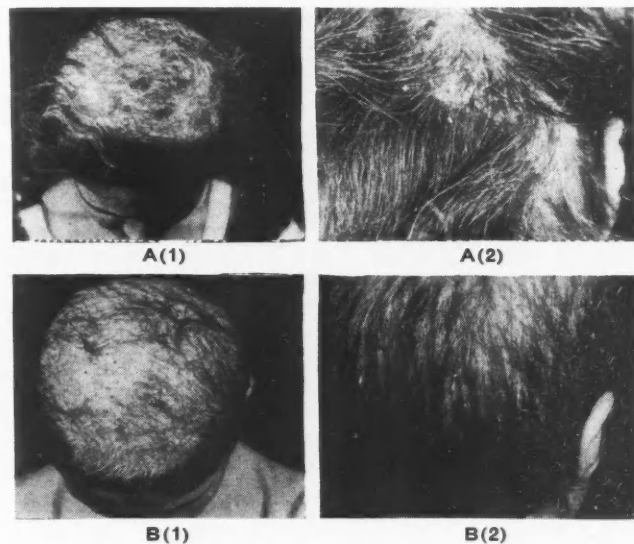


Fig. 1.—Favus of 22 years' duration caused by *T. schönleini*. A(1) and A(2), before treatment; B(1) and B(2), after 14 weeks with oral griseofulvin (1.0 g. daily).

established by culture. The etiological agent was *M. canis* in 19, and *M. audouini* in two. Good results were obtained in all but two, who showed no improvement after two weeks.

Parents were advised to cut the hair very short or, better, to shave the hair every two weeks and also to give a shampoo twice a week.

Mycological examinations were made, in most cases, every two weeks.

TABLE IV.—DERMATOMYCOSES AND GRISEOFULVIN

Variety of mycoses	Number of patients	Organism	Daily dose	Duration of treatment	Results
Tinea cruris	4	<i>E. floccosum</i> (2) Not isolated (2)	1.0 g.	2 to 5 weeks	No pruritis after three to five days. Marked clinical improvement in two patients. Clinical cure in two others. One of them has a negative culture after three weeks.
Tinea pedis	3	<i>T. rubrum</i> (2) Not isolated (1)	1.0 g.	4 weeks	No pruritus after one to two weeks. Clinical cure in three weeks, in two patients. Very little improvement in the other.
Tinea corporis	8	<i>T. mentagrophytes</i> (4) <i>M. canis</i> (2) Not isolated (2)	1.0 g.	2 to 5 weeks	Clinical and mycological cure in two patients in three weeks, and in four patients in five weeks. Marked clinical improvement in two other patients.

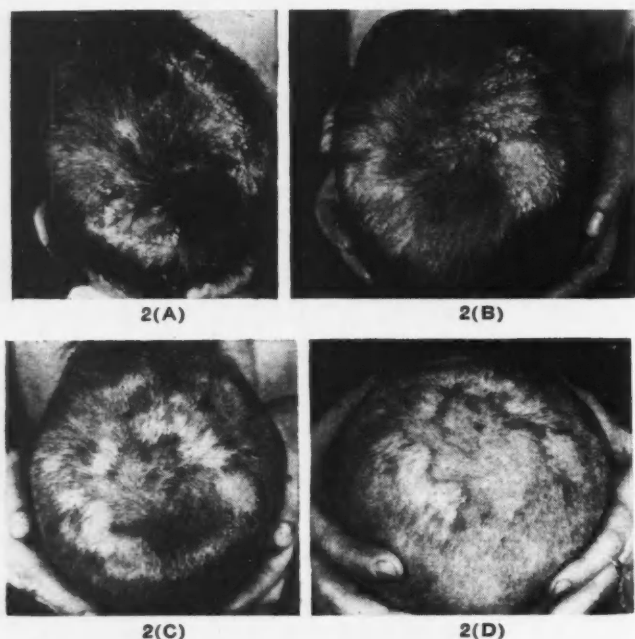


Fig. 2.—Favus of 6 years' duration caused by *T. schönleini*. A, before treatment; B, after 3 weeks of treatment; C, after 6 weeks of treatment; D, after 9 weeks of treatment.

TABLE V.—ONYCHOMYCOSIS AND GRISEOFULVIN

Organism	Number of patients	Nails involved	Duration of disease (years)	Daily dose	Duration of treatment	Results
<i>T. rubrum</i>	2	4 nails (left hand)	10	1.0 g.	13 weeks (treatment continued)	Nails almost completely normal.
		2 nails (medial aspect of each hand)	1/2		3 weeks (treatment continued)	1/4 of the nail plate normal.
<i>T. schönleini</i>	1	left thumb	10	1.0 g.	5 weeks (treatment continued)	More than 1/2 of the nail normal.
Not isolated	1	5 nails (hands)	1/2	1.0 g. (5 w.)	12 weeks (treatment continued)	Nails almost completely normal. Toe nails: only 1/4 of the nail plate is normal.
		10 nails (feet)		0.75 g. (5 w.) 0.50 g. (2 w.)		

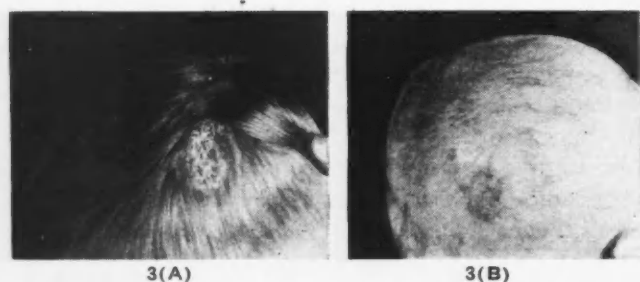


Fig. 3.—Favus of 4 months' duration caused by *T. schönleini*. A, before treatment; B, after 4 weeks of treatment.

The two children with *M. audouini* infection showed a negative Wood's lamp examination after two and four weeks. Clinical cure was obtained in nine weeks, but one still had a positive culture.

Of the other 19 children with *M. canis* infection, 17 improved during the first two or three weeks of treatment, with increase in the scaling and absence of fluorescence in the proximal portion of the hair. A completely negative Wood's lamp examination took place between 2 and 7 weeks, averaging 5½ weeks.

In one case, a recurrence was seen one month after treatment was discontinued.

The other five patients treated from two to eight weeks showed marked clinical improvement. Fluorescence is absent in two and much decreased in three.

Daily dosage of 20 to 30 mg. of griseofulvin per lb. body weight seemed as effective as a higher dosage.

TINEA CRURIS, PEDIS AND CORPORIS AND GRISEOFULVIN (TABLE IV)

Tinea cruris

Four patients with tinea cruris, which varied in duration from two to five weeks, were treated by a daily dose of 1.0 g. of griseofulvin. In two of these patients, the organism was *Epidermophyton floccosum*.

Pruritus ceased in three to five days, and marked clinical improvement was seen after a week in all instances.

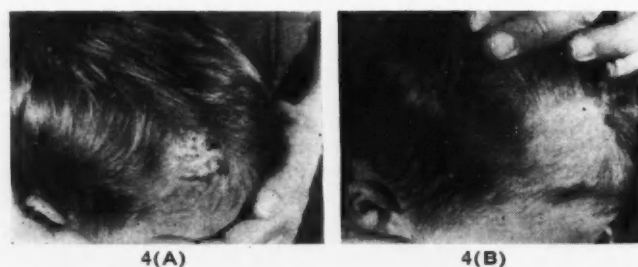


Fig. 4.—Tinea capitis of 3 months' duration, caused by *M. audouini*. A, before treatment; B, after 9 weeks of treatment.

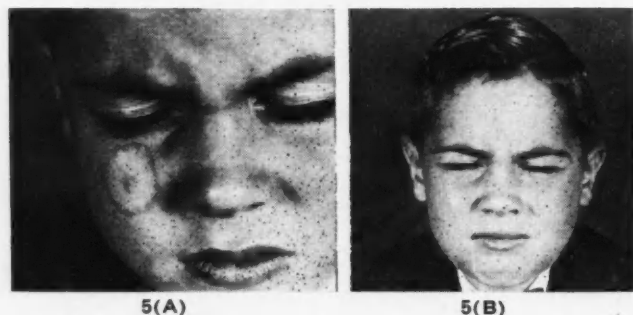


Fig. 5.—Tinea corporis of 4 weeks' duration, caused by *T. mentagrophytes*. A, before treatment; B, after 2 weeks of treatment.

Two patients were clinically cured in three weeks, and one of them had a negative culture.

The other two patients were greatly improved.

Tinea pedis

Three patients with tinea pedis were treated by griseofulvin (1.0 g. daily). In two, the disease was due to *T. rubrum*.

Itching disappeared in one to two weeks. After four weeks of treatment there was clinical cure in two and improvement in the other.

Tinea corporis

Eight patients with tinea corporis were treated by 1.0 g. of griseofulvin daily. Four of these patients had *T. mentagrophytes* infection, and two had *M. canis* infection. The fungus was not identified in the other two patients.

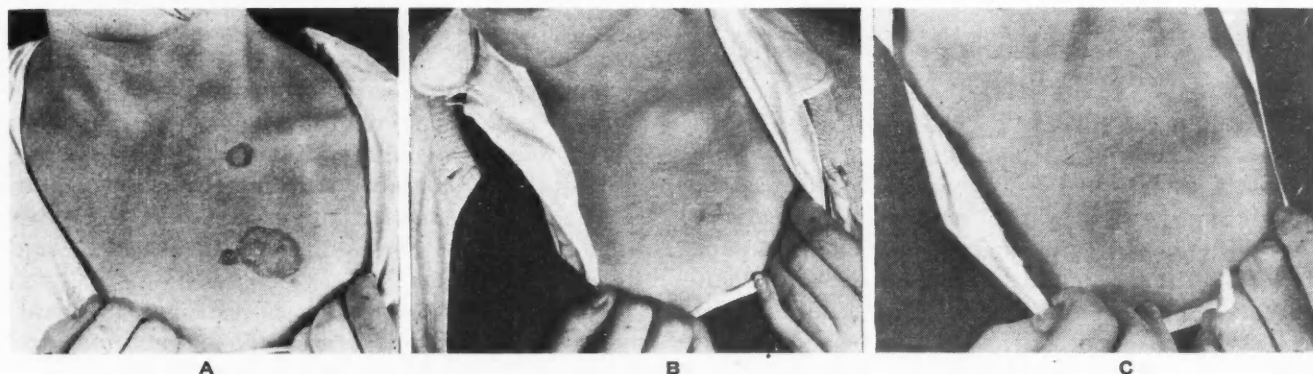


Fig. 6.—Tinea corporis of 3 weeks' duration, caused by *T. mentagrophytes*. A, before treatment; B, after 2 weeks of treatment; C, after 4 weeks.

A clinical cure was obtained in two cases by three weeks, and in four cases by five weeks.

Two other patients, treated for only two weeks, showed great improvement. None of these 14 patients with tinea received topical treatment.

ONYCHOMYCOSIS AND GRISEOFULVIN (TABLE V)

Four patients with onychomycosis were treated with 1.0 g. of griseofulvin daily. This condition was of six months' duration in two patients and of ten years' duration in the others. It was due in two cases to *T. rubrum* and in one to *T. schönleini*.

In spite of the marked variation in the duration of the disease and the different etiological agents, all patients responded uniformly well to griseofulvin. After two or three weeks, infected nails showed a certain degree of normal regrowth.

The two patients under treatment for 13 weeks have practically normal nails. In one of them the culture is negative. Improvement of toe nails is much slower: after 13 weeks of treatment, half of each nail is still infected.

The other two patients, treated for three to five weeks, showed about a quarter to a half normal nail plate.

In order to insure complete healing without recurrence, treatment will have to be continued for many weeks.

TOXICITY

One adult patient, who received 1 g. of griseofulvin daily for seven weeks, complained of severe headache; termination of treatment was followed by almost immediate relief. Another who had the same trouble, obtained relief when the daily dose was reduced to 0.5 g.

Temporary loss of appetite was observed in two children, but discontinuation of griseofulvin was not necessary.

COMMENTS

Oral griseofulvin was effective in the treatment of 47 patients suffering from superficial mycoses.

Its action seems to be related to its incorporation into the keratinized tissues of the skin, hair and nails. Presence of the antibiotic in guinea-pig hair has been demonstrated by Gentles.⁷

Bedford *et al.*⁸ were able to detect its presence in the blood, peak levels being obtained four hours after a single dose.

The effect of griseofulvin is to prevent reproduction of the dermatophytes and elimination of them by increased desquamation. Its fungistatic action is due to its accumulation in keratinized tissues; topical application has been almost useless.

In the course of treatment of tinea capitis a sharp line of demarcation soon appears between the infected portion of the hair and the new portion. This is well demonstrated by the Wood's lamp and by microscopic examination.

The new portion of hair is protected against the dermatophytes. These show morphological modification due to the "curling factor".

We have observed that in some cases it became more and more difficult to obtain typical colonies of the fungus. Colonies of *T. rubrum* are less pigmented, and those of *M. canis* grow less quickly and present much less "fuseaux". Colonies of *T. schönleini* grew mainly into the agar. All these modifications disappear after two or three subcultures.

To facilitate isolation of dermatophytes, corn meal agar or Sabouraud's medium was used together with a medium such as Littman's or acti-



Fig. 7.—Onychomycosis of 10 years' duration, caused by *T. rubrum*. A, before treatment; B, after 13 weeks of treatment.

dione-containing media, in order to restrain invasion of the culture by penicillia.

Results of treatment of favus were very good, though improvement was rather slow in comparison with that reported by Degos *et al.* One gram of griseofulvin daily should be the dosage, and treatment should be maintained for three months, and in some cases five months. Dosage can be reduced to 0.5 g. after six to eight weeks if patients weigh less than 40 kg. It must be emphasized that a treatment for three months or more is important in order to avoid possible relapse or reinfection. One of our patients⁴ had such a reinfection two months after treatment was discontinued and cultures were negative. Atrophy of the scalp, with secondary permanent alopecia, seems also to require longer treatment, which will result in a definite cure.

Six of our seven patients with favus belonged to a family in which 24 members are known to suffer from this disease. There would appear to be some

kind of individual immunity against *T. schönleini* since some of the children living in the same house, and in daily contact with infected brothers or sisters, have remained unaffected. On the other hand, the disease does not appear to spread beyond the immediate family.

Griseofulvin was equally successful in the treatment of tinea capitis caused by *M. audouini* and *M. canis*. The daily dose varied from 20 to 30 mg. per kg. of body weight, and a higher dose was no more effective.

Hair fluorescence disappeared after two to seven weeks in 19 of 21 patients. The duration of treatment, ranging from five to twelve weeks, varied with the individual, being based on clinical examinations and mycological findings.

As suggested by Kirk and Ajello,⁴ two negative cultures were a criterion of definite cure. These authors have observed that when the infection had lasted a year or more, the healing period seemed



Fig. 8.—Onychomycosis of 6 months' duration, caused by *T. rubrum*. A, before treatment; B, after 9 weeks of treatment.

shorter. This would explain the slow rate of improvement we obtained, as most of our patients with tinea capitis had been infected only four to six weeks. Also, hair cutting or shaving, though strongly recommended to the patients, was not always carried out.

The recurrence of infection in one patient a month after cessation of the treatment would seem to indicate that, in most cases of tinea capitis, topical treatment should be given in association with oral griseofulvin. The same would apply to patients with favus. X-ray epilation is no longer necessary.

The 15 patients with dermatomycoses responded well to griseofulvin. In these cases, the antibiotic should be given for three or four weeks or more, at a daily dosage of 1 g. Griseofulvin produced relief of subjective symptoms in three to five days in patients with tinea cruris, and in one to two weeks in patients with tinea pedis.

Topical fungicidal preparations would probably shorten the duration of treatment with griseofulvin. In some cases of tinea corporis due to *T. mentagrophytes* and *M. canis*, topical treatment alone

would have been as effective as its use in association with oral griseofulvin.

Onychomycosis caused by *T. schönleini* or *T. rubrum* was successfully treated by griseofulvin. A much slower rate of improvement of toenail infection, mentioned by some authors, was observed by us. Though the treatment of onychomycosis by griseofulvin is likely to last from four to six months, this drug is remarkable if we consider that it is the first really effective medication for this condition.

Griseofulvin is of great efficacy and low toxicity and is the most important advance in dermatological therapy in recent years.

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USE OF IMIPRAMINE (TOFRANIL) IN PSYCHIATRIC PATIENTS OF A GERIATRIC OUTPATIENT CLINIC*

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THE BENEFICIAL effect of imipramine in the treatment of certain types of depressive conditions has been described by a number of authors.¹⁻³ The highest improvement rates were found in hospitalized patients suffering from "endogenous" depressions (Kuhn 70-80%, Kielholz 60%, Azima 83%). Sarwer-Foner and co-workers,⁴ on the other hand, found only a 50% improvement rate in patients who were suffering largely from neurotic depressions and were treated in open psychiatric settings.

Although the pharmacology of imipramine has been extensively discussed by Häfliger⁵ and Sigg,⁶ general agreement has not been reached regarding its psychophysiological properties and psychological effects. Lehmann, Cahn and de Verteuil⁷ showed that the drug tended to inhibit perceptual, psychomotor and cognitive functions, but seemed to increase word fluency. Azima,⁸ who studied the psychodynamic alterations concomitant with imipramine administration, expressed the opinion that it

produces a change of aggressive drives from inward to outward, a secondary reorganization of libidinal tendencies, a decrease in guilt feelings and a change from preoccupation with internal to external object relationships. Sarwer-Foner and his collaborators, though reporting similar findings, added that these changes are obtained in any patients recovering from a depression under any form of treatment.

Whatever the mechanism underlying its clinical effect, improvement rates as reported by the various authors were high enough and the incidence of side effects so low that the use of imipramine in geriatric practice appeared warranted. Cameron⁹ reported on the favourable effect of imipramine in aged persons. He found that in patients of this age group it alleviated the rather unspecific mood disturbance, the chief characteristics of which are depression, withdrawal, irritability and affective swings. The favourably affected patients showed a return in activity, interest, memory and judgment.

It is the purpose of this paper to report on the results of a clinical assessment of imipramine carried out from January 1 to December 31, 1959, in selected case material of a geriatric outpatient clinic, the organization and operation of which has been described previously.¹⁰ Patients over 60 years of age are eligible to attend this clinic. They and their families are first seen by the social worker, who takes the social history. The patient's condition is assessed by the psychiatrist and by the

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medical section of the clinic. Psychological testing is a routine part of the investigation; the test battery consists of the Rorschach, Wechsler-Bellevue and Bender Gestalt tests, depending on the clinical problems. Patients are seen once weekly at the start of treatment, and at longer intervals later. Long-term contact is maintained where necessary.

CASE MATERIAL AND METHOD

Imipramine was given to 33 patients (4 men and 29 women) suffering from depressive states, some of whom had previously been treated by other methods. Patients in this series did not receive ECT (electroconvulsive therapy) while receiving imipramine. Fifteen patients, however, received low doses of other drugs in addition to imipramine (meprobamate—7 cases; perphenazine—4 cases; chlorpromazine—3 cases; phenobarbital—1 case) in order to avoid agitation or to diminish anxiety. Twelve patients needed night-time sedation which consisted of small doses of barbiturates. Patients previously receiving psychotherapy continued with it while taking imipramine. Contacts with the patients' relatives were maintained, and case work therapy by the social worker was continued or initiated with relatives wherever it was felt that this would be of benefit to the total treatment regimen. Twenty-three of the patients treated were also being followed up on the medical side of the clinic and received appropriate medication for their medical condition.

The effect of treatment was evaluated by clinical observation in interviews with the patient by one of the authors (H.G.) and where possible also by obtaining the opinion of a closely associated relative or friend. The weight and blood pressure values were recorded at each clinic visit.

Table I shows the age distribution of our case material. The age range was 60-85 years, the average age being 70.7.

TABLE I.—AGE DISTRIBUTION

Age group	Number of cases
60 - 64.....	4
65 - 69.....	8
70 - 74.....	16
75 - 79.....	3
80 - 85.....	2
	33

Table II shows the duration of treatment. The average duration was 5.4 months. All patients received the drug *per os*. Dosage ranged from 25 mg. to 150 mg. daily; the average daily dose was 98 mg.

Table III gives the distribution of our material as to diagnostic categories. A brief comment seems necessary regarding the group of reactive depressions shown in the diagnostic categories. These were divided into an acute and a chronic subgroup. In three out of the six classed as acute—that is, of

TABLE II.—DURATION OF TREATMENT

	Number of cases
7 days.....	1
14 ".....	2
21 ".....	2
28 ".....	2
1 - 2 months.....	3
2 - 4 ".....	4
4 - 6 ".....	5
6 - 8 ".....	4
8 - 10 ".....	7
10 - 12 ".....	3
	33

less than one year's duration—loss of a loved object, such as a spouse, was the traumatizing factor; loss of means of support was the factor in two; reaction to anniversaries, of individual symbolic meaning, in one. This was a 78-year-old, married woman who had been depressed for three years in succession at the time of the Jewish High Holidays. On two occasions she had been treated with imipramine.

TABLE III.—DIAGNOSIS

Reactive depression:.....	15
(a) Acute.....	6
(b) Chronic.....	9
Depressive reaction in a passive-dependent personality..	2
"Endogenous" depression.....	5
Chronic brain syndrome (secondary to cerebral arterio-sclerosis or senile brain disease) with depressive features.....	9
Compulsive personality disorder with depressive features	1
Conversion reaction (chronic) with depressive features...	1
	33

The chronic reactive depressive group comprised nine cases. Here the depression lasted more than one year. The loss of loved objects (spouse and child in one case; loss of one child in two cases) and a reaction to physical illness and lost physical integrity in six, formed the factors to which the patients reacted by a depression.

The major medical diagnoses grouped by organ systems are given in Table IV.

TABLE IV.—MEDICAL DIAGNOSIS GROUPED BY ORGAN SYSTEM

Cardiovascular.....	4
Vascular.....	1
Bronchopulmonary.....	1
Gastrointestinal.....	1
Musculoskeletal.....	7
Endocrine.....	6
Eye.....	1
Nutritional deficiency.....	1
Central nervous system (basal ganglia disease).....	1
Psychiatric illness only.....	10
	33

RESULTS

Weight.—The last weight obtained after treatment was compared with the weight before beginning treatment. Table V shows the changes in weight. These data indicate that there was no definite trend to either weight gain or weight loss in the patients as a group.

TABLE V.—CHANGE IN WEIGHT

Loss of 10 - 15 lb.	1
" 5 - 10 "	4
" 0 - 5 "	9
No change	3
Gain of 0 - 5 lb.	9
" 5 - 10 "	2
" 10 - 15 "	1
	29

Blood pressure.—The mean blood pressure readings before starting therapy were compared with the average blood pressure readings obtained while the patient was under treatment. Table VI shows that imipramine has a definite tendency to lower both the systolic and the diastolic blood pressure.

TABLE VI.—CHANGE IN BLOOD PRESSURE

	Systolic	Diastolic
Decrease in mm. Hg -40	3	1
-20 -40	4	1
-15 -20	1	2
-10 -15	2	2
- 5 -10	3	5
0 - 5	3	2
No change	7	7
Increase in mm. Hg 0-10		4
10-15	2	5
15-20	2	1
20-40	1	1
40	1	
	29	31

Side effects.—Table VII lists the main side effects observed in our patients.

TABLE VII.—SIDE EFFECTS

	Number of cases
Dizziness	2
Sweating	2
Constipation	2
Dryness of mouth	3
Agitation	1*

*This patient received only imipramine; a neuroleptic was not used.

Patients treated less than 14 days.—Table VIII gives a brief account of the three patients who took imipramine for 14 days or less.

Assessment of the therapeutic results was based on changes in mood, changes in energy output and improvement in object relationships, sleep, appetite, overall activity and interpersonal relations.

TABLE VIII.—ANALYSIS OF CASES IN WHICH TREATMENT WAS FOR LESS THAN TWO WEEKS

Case 24:	ECT was started after there was no evidence of improvement after a 14-day trial of the drug.
Case 28:	Patient discontinued treatment after two weeks. This patient has become depressed three years in succession at the time of the Jewish High Holiday and usually quickly recovers once the holiday season has passed.
Case 31:	Because of severe constipation, patient refused to take drug after one week's trial.

Table IX evaluates the therapeutic results from the standpoints of the doctor, the patient and the relatives where available. It was impossible to interview the relatives of eight patients. The lack of concordance seen in some instances is explained by the fact that the patient or his relatives often expected a vast improvement from a "new drug". This was seen particularly in patients with the diagnosis of chronic brain syndrome with depression.

TABLE IX.—THERAPEUTIC RESULTS

According to patient: Improved	15
Same	15
Worse	3
	33
According to doctor: Improved	17
Same	14
Worse	2
	33
According to relative: Improved	14
Same	8
Worse	3
	25

Table X illustrates the therapeutic results in relationship to the diagnosis. The numerator is the number of patients who improved while the denominator shows the total number of cases in that diagnostic category.

TABLE X.—RELATION OF DIAGNOSIS TO THERAPEUTIC RESULTS

	Doctor rating	Patient rating
Reactive depressions: (a) acute	6/6	3/6
(b) chronic	3/9	1/2
Depressive reaction in a passive-dependent personality	1/2	4/5
"Endogenous" depression	4/5	4/5
Chronic brain syndrome (secondary to cerebral arteriosclerosis or senile atrophy) with depressive features	3/9	2/9
Compulsive personality disorder with depressive features	0/1	0/1
Conversion reaction (chronic) with depressive features	0/1	0/1

DISCUSSION

Approximately 50% of the patients showed definite clinical improvement. This is in agreement with the results reported by Sarwer-Foner and his collaborators in patients of a younger age group in similar settings. The patients who benefited most in the present series were those suffering from "endogenous" and reactive depressions. Four out of five patients with "endogenous" depression improved. This group includes one patient with manic-depressive psychosis, depressed phase. This patient improved. Two-thirds of those with reactive depressions also improved. It is interesting to note that all six patients with reactive depression of less than one year's duration improved, but only three out of nine in the group where the duration

was more than one year. This difference was particularly marked when the rate of improvement was assessed by the doctor, but was not so clear in the patient's own evaluation. This lack of concordance between the physician's and the patient's evaluation of the benefit obtained by the drug in the group of acute reactive depressions could possibly be explained by the assumption that the patient is still going through a period of mourning while clinically he may already appear improved. Patients with a depression associated with chronic brain syndrome or with marked personality disorder had relatively poor results. Less than one-third of them improved.¹¹

Patients who benefited showed an elevation in mood and an increase in energy output and activity. A number of patients showed renewed interest in object relationships. Before treatment, interest was self-centred, which was often manifested by increased somatic complaints and unrealistic expectations from treatment and medication. After treatment the patients became more out-going, more interested in their household, family and friends and less involved with themselves.

Side effects were minimal and did not interfere in any of the patients receiving treatment. Only one patient refused to continue the drug because she became markedly constipated. There was some tendency for the drug to produce hypotension, but in this series it was not found necessary to discontinue treatment for this reason. Data published by Mann, Catterson and MacPherson¹² and

Sloman¹³ suggest the need for caution when giving this drug to patients who have cardiovascular disease. In this series, however, no major difficulties were encountered in this respect. It is the impression of the staff that the use of this drug decreased the number of electroconvulsive treatments prescribed during the year in the treatment of this particular condition.

SUMMARY

Imipramine proved to be a useful, relatively safe adjuvant in the treatment of depressive states in the aged. It is suitable for the treatment of "endogenous" as well as reactive depression in this age group.

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REVIEW ARTICLE

LES VIRUS DANS LES INFECTIONS DES VOIES RESPIRATOIRES

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LA PREMIÈRE PARTIE DE DEUX PARTIES

LES INFECTIONS des voies respiratoires, aussi bien chez les adultes que chez les enfants¹ sont très fréquentes. Selon Horsfall² "70% des maladies infectieuses observées sont des infections respiratoires et 90% de ces infections sont dues à des virus; cependant, un petit nombre de ces virus sont connus aujourd'hui. Heureusement, plusieurs de ces maladies sont bénignes et de courte durée. D'autre part, l'emploi des antibiotiques n'influence pas le cours et la fréquence de ces infections virales; de même la mortalité, le cas échéant, ne se trouve pas diminuée. Il est étonnant de voir la quantité d'antibiotiques donnée dans ces cas chaque année, dans le but plus ou moins justifiable de protéger le patient contre des infections bactériennes secondaires, et quand de plus, la sévérité de ces complications que l'on observe semble s'accroître."

Au point de vue clinique, ces infections peuvent prendre les formes les plus diverses; à savoir un simple coryza nasal, une sinusite, une pharyngite plus ou moins prononcée, avec ou sans présence de vésicules, et accompagnée ou non de conjonctivite, une laryngo-trachéo-bronchite, une bronchite, une broncho-pneumonie ou pneumonie, voire même une pleurésie. L'agent bactérien, comme cause étiologique dans plusieurs de ces syndromes est bien connu aujourd'hui. De plus, on sait que des espèces différentes de bactéries peuvent être la cause d'un même syndrome clinique et que même malgré les théories immunitaires, on peut assister fréquemment à des récives ayant comme agent étiologique la même espèce bactérienne. Par exemple, des amygdalites ou pharyngites à *Streptococcus* hémolytiques peuvent récidiver chez le même individu. Bien entendu, pour sauvegarder le principe immunitaire, on peut faire appel à une grande variété de sérotypes parmi les espèces. Cependant, il est courant en bactériologie de dire que les infections à *Streptococcus* ainsi qu'à *Staphylococcus* et en général, les infections à microbes pyogènes ne laissent aucune immunité valable après leur passage chez un individu. En effet, il n'existe aucun vaccin utilisé couramment en vue de la prophylaxie de ces infections.

S'il existe des bactéries capables de causer des maladies bien différenciées dites spécifiques, telles

la diphtérie ou la typhoïde, aussi y a-t-il des virus capables de provoquer des syndromes bien définis, tel la rage. Cependant ces maladies sont de loin celles que les cliniciens ont à envisager tous les jours; au contraire, ce sont plutôt les infections à microbes banaux communément dénommés pyogènes. Ceux-ci ont la propriété de causer des tableaux cliniques infectieux très variés ou indifférenciés. Par conséquent, il faut s'attendre en virologie à rencontrer des virus dont le comportement pathogénique s'apparente à ces bactéries pyogènes et même on pourra se retrouver vis-à-vis de virus qui sembleront provoquer des infections à répétition chez un même patient. Alors pour étiqueter comme il se doit et de façon scientifique, ces syndromes infectieux, et ainsi apprécier les répercussions qu'ils peuvent avoir sur la santé ultérieure de l'individu, on doit faire suivre l'infection clinique du nom de l'agent infectieux soit bactérien ou viral en cause.

Les cliniciens possèdent deux moyens pour arriver à l'identification exacte de l'agent viral en cause. En premier lieu, ils doivent essayer, dans ces syndromes infectieux à étiologie multiple, de retracer dans l'entourage du patient, des épisodes fébriles cliniques plus ou moins évidents et qui l'orienteront vers un agent étiologique précis. En deuxième lieu, ils feront appel au laboratoire soit pour leur fournir l'information qui leur manque, soit pour les confirmer dans leur enquête épidémiologique.

Dans les infections, une étiologie virale doit être soupçonnée cliniquement par les signes suivants:³ une courbe de température diphasique qui se produit dans les cas où il y a propagation septicémique avec deux endroits distincts de multiplication virale; la présence d'une leucocytose quasi normale, ou d'une leucopénie avec prédominance de lymphocytes; ou la présence de réactions lymphocytaires dans le liquide céphalorachidien; soit d'autres signes généraux d'infection virale, tels que des adénopathies généralisées, une courte période d'incubation, et une haute contagiosité.

Si au laboratoire, on peut expliquer un grand nombre d'infections respiratoires à virus durant une période épidémique, au contraire, on obtient un pourcentage d'isolements positifs faible, lorsqu'en temps normal, on recherche les divers agents viraux susceptibles de causer ces infections. Aussi, il faut le dire, il est impossible de mettre en branle toutes les techniques d'isolement des virus respiratoires connus, en vue d'obtenir un résultat positif pour tel virus dans un cas et tel autre virus dans un autre, et parfois sans à enlever avoir au préalable aucun signe d'orientation. Malgré tout, l'utilisation des cultures de tissu en couche monocellulaire et l'inoculation des spécimens pathologique préalablement traités par les antibiotiques sur deux types différents de cellules, à savoir, les cellules de rein

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de singe et les cellules Hela, nous permettent d'arriver à l'isolement d'une grande variété de virus banaux, c'est-à-dire, provenant de maladies plus ou moins différenciées.

VIRUS RESPIRATOIRES CONNUS

Parmi les virus susceptibles de causer des infections respiratoires, il y a d'abord les Entérovirus. Les virus poliomyélitiques peuvent se limiter au tractus respiratoire et causer de véritables épidémies de maladies respiratoires aiguës, ceci a déjà été observé pour le type II.⁴ Les virus Coxsackie A causent des pharyngites vésiculeuses qu'on dénomme herpangine; les virus Coxsackie B, eux aussi peuvent comporter comme signes cliniques prédominants, parfois sans aucun autre signe, des symptômes respiratoires, voire même de simples sinusites

Parmi les Myxovirus, on rencontre un groupe nouvellement formé du nom de Parainfluenzae, suggéré par Andrews et coll.⁶ Le tableau I nous donne une vue d'ensemble des prototypes de ces virus et des souches isolées qui présentent une certaine parenté, voire une identité antigénique vis-à-vis de ces prototypes. Dans ce tableau, nous remarquons que ces virus ont un diamètre de 100m μ environ et qu'ils sont tous détruits par l'éther à la concentration de 20%, propriété générale des Myxovirus. Le groupe Parainfluenzae I comprend le virus H.V.J. ou Sendai, dénommé aussi Influenzae D, qui cause des pneumonies sévères, avec réactions méningées parfois, chez les nourrissons et rencontré surtout au Japon.^{7, 8} Le virus Hémadsorption HA-2⁹ rapporté comme agent étiologique dans des cas de laryngo-trachéo-bronchite et mis en évidence

TABLEAU I.—PARAINFLUENZA

Virus	Diamètre m μ	Résistance à éther	Cellules				Dégéné- rescence	Œuf incubé	Souri- ceaux	Héماغ. poulet- cobaye	Héماغ- sorption i.d.	Rec. G.R. détruit par		I.H.	C.F.	Neut.	Symptômes
			R.S.	Hela	Am- nios	K.B.						Virus	RDE				
Para. I H.V.J. ou Sendai		0	?				?	+		Œuf: + 30 min. Cellules: ?			+	+	+	Souris I.N.	Pneumonie nourrisson X oreillons
HA ₂		0	+				Légère	+		Œuf: + Cellules: +	+		+	+	+		Croup?
Cop. 222		0	+	0	0		Légère	0		Cellules: +							Grippe
Para. II CA	90 à 135	0	+		+		Syncytium Sponge-like Swiss cheeselike	+ 5 jrs	0	Œuf = 0 ou + Cellules = + 4°C 4°C→37°C=0		Faible	+	Inc. 2 hrs. 25° avant G.R.	+	Facteur thermo- labile >1/16= sig.	Croup X oreillons
Para. III HA ₁		0	+				Légère	+		Œuf = + Cellules = +	+		+	+	+		Mal. resp. enfant
EA-102	80 à 100	0	0 mult. +	+		+	Syncytium noyau visible	0	0	Cellules=0	+						Mal. féb. nourrisson

maxillaires; sans parler, bien entendu, de la maladie de Bornholm ou myalgie épidémique. Les virus ECHO et plus particulièrement les types 8, 10, 20 ont déjà été rapportés comme cause d'infections respiratoires aiguës. Cependant à côté de ces virus qui sont rencontrés plus particulièrement vers la fin de l'été et à l'automne, il existe un groupe de virus qu'on rattache plus particulièrement au tractus respiratoire; ce sont les Myxovirus.

Bien entendu, tous connaissent le tropisme particulier des trois grands types de virus de l'Influenza et du dernier venu, le sous-type A, asiatique. Les Myxovirus ont la propriété d'être prévalents durant les saisons intermédiaires, l'automne et le printemps. L'isolement des virus de l'Influenza par la technique classique de l'inoculation intra-amniotique des sécrétions pharyngées chez l'embryon de poulet peut se faire aujourd'hui sur culture de tissu en tubes; dans ce dernier cas, on peut observer soit l'action cytopathogène, soit l'action hémadsorbante ou hémagglutinante des virus Influenza A et B. Cependant le virus Influenza C se cultive dans la cavité amniotique de l'œuf embryonné et ne possède pas la propriété de se multiplier dans les cultures cellulaires en tubes.⁵

par la technique d'hémadsorption décrite par Shelokov¹⁰ ainsi que le virus Cop 222¹¹ isolé dans des cas de grippe. Ces virus appartiennent tous au groupe Parainfluenzae I. Le virus C.A.¹² fait partie du groupe Parainfluenzae II et il a été trouvé associé au croup¹³ chez les jeunes enfants; de plus son action cytopathogène sur les cellules de rein de singe ou d'amnios humain est bien caractéristique. Enfin, le groupe Parainfluenzae III comprend le virus Hémadsorption HA-1⁹ et la souche EA-102¹⁴ qui sont, semble-t-il, la cause de maladies fébriles respiratoires chez les nourrissons.¹⁵ Ce groupe de virus classé sous le nom de Parainfluenzae présente des parentés antigéniques entre eux et aussi avec le virus des oreillons et le virus de Newcastle.¹⁶

Il existe d'autre part, en dehors des Myxovirus, Influenzae et Parainfluenzae plusieurs virus nouvellement isolés qui présentent peu de cohésion entre eux et qui sont à l'origine d'infections des voies respiratoires. D'abord, les virus JH-1¹⁷ et 2060¹⁸ ou JH-2^{19, 20} qui s'apparentent de très près avec les virus ECHO et sont capables de provoquer expérimentalement chez l'homme²¹ une maladie ressemblant au rhume commun. Ils ont été isolés surtout

chez les adultes présentant des épisodes infectieux respiratoires bénins et de courte durée.²² Il y a le groupe Réovirus²³ nom donné récemment aux virus ECHO type 10, qui ont un diamètre supérieur aux virus ECHO et dont la dégénérescence en culture de tissu est caractéristique; il existe trois types distincts dans ce groupe et ils présentent une affinité pour les tractus; respiratoire et intestinal.

Il ne faut pas oublier le virus Coe qui a été isolé par Lennette²⁴ et ses collaborateurs en 1958, chez des adultes présentant des pharyngites bénignes. Aussi il y a le virus Long isolé chez les enfants par Chanock et coll.,²⁵ en 1957; il présente une parenté antigénique avec le C.C.A. virus,²⁶ c'est-à-dire, l'agent du coryza du chimpanzé. Chanock²⁷ suggère de nommer ces virus "RS", "virus syncytial respiratoire". Enfin, il y a deux autres virus, qui ont été isolés dernièrement chez des sujets souff-

général malgré des signes radiologiques parfois alarmants. Dans de nombreux cas, une infection spécifique sera soupçonnée devant un tel tableau, à savoir la tuberculose pulmonaire ou la fièvre typhoïde. Dans les pneumonies à virus P.A.P., la présence des hémagglutinines à froid³⁴ et la recherche des agglutinines pour le Streptococcus MG^{35, 36} ainsi que la vitesse de sédimentation accrue³⁷ orienteront le diagnostic. S'il s'agit d'une pneumonie à Adénovirus, on devra rechercher à le prouver en tentant l'isolement du virus à partir des sécrétions pharyngées ou des selles et en recherchant l'augmentation significative des anticorps de groupe, fixateurs du complément, ou de type, neutralisants.

Si les infections pulmonaires d'origine virale ont pu être individualisées assez tôt en clinique, les infections bénignes respiratoires (A.R.D.)³⁸ ont pu

TABEAU II.—AUTRES VIRUS (MALADIES RESPIRATOIRES)

Virus	Diamètre μ	Résistance à l'éther	Culture cellules				Dégéné- rescence	Œuf incubé	Souri- ceaux	Hémagglu- tinines	Hémod- sorption	Rec. G.R. détruit par		I.H.	C.F.	A.N.	Symptômes
			R.S.	Hela	Amnios	K.B.						Virus	RDE				
JH ₁	40-20	+	+ 2e pas ph 7.9	0		0	Rondes, gonflées	0	0	0 Nécessité de trypsiniser GR poulet					+	+	Adultes mal. légère 3 jrs
2060 ou JH ₂	40-26	+	+ 2e pas	0		0	Rondes, gonflées	0	0	0 Nécessité de trypsiniser GR poulet					+	+	Recrues mal. légère
Réovirus ECHO-10 3 types	75	+	+				Granuleux Noyau intact	+	Cerveau myocarde foie Rare muscle	GR humain 0 seulement		0 Nal ₀₂ détruit		type	groupe	type	
COE	20	+	0	+ 6 jrs		+	Rondes, gonflées	0	Paralyse lég. pas réinocu- lable	0					+	+	Pharyngite
LONG	? 90-130	0	0		0	+ 8 jrs 3 jrs	Syncytium et cellules rondes	0	0	0					+	+	× C.C.A. ou id Mal. resp. enfants
SA (myovirus)		0	+	+			Syncytium	+		+	+	+	+		+	+	Mal. resp. sévère

frants de maladies respiratoires et qui possèdent les propriétés générales des Myxovirus. Ce sont le virus "SA"²⁸ et le virus M-25;²⁹ celui-ci s'apparente plutôt aux virus Hémodsorption. Le tableau II donne les principales caractéristiques biologiques de ces virus sur les diverses cultures de tissu et sur l'œuf embryonné, couramment employés en virologie.

Je passerai sous silence les atteintes du tractus respiratoire par les virus de la Chorioméningite lymphocytaire, et de la Psittacose, pour m'attacher plus particulièrement à deux virus plus répandus: le virus de la P.A.P.,^{30, 31} et les Adénovirus.³² Ces virus sont reconnus pour provoquer cliniquement des atteintes pulmonaires³³ plutôt décelables par la radiographie. Le début de ces infections est graduel et insidieux, accompagné de toux sèche, de céphalée, d'anorexie et de diaphorèse. La formule leucocytaire est ordinairement normale ou légèrement élevée et le patient présente un bon état

être distinguées des infections microbiennes tout dernièrement. L'étude de ces infections, qui la plupart du temps demeurent d'un pronostic bénin, a été faite après la dernière guerre mondiale et cette étude a porté surtout chez des militaires. Il semble que ces infections seraient rares dans la vie civile. Alors, cette constatation est-elle conforme à la réalité, ou dépend-elle d'une recherche plus méticuleuse orientée dans un groupe particulier? En effet, les publications concernant le virus P.A.P. chez les jeunes enfants sont inexistantes,³⁹ et celles concernant les Adénovirus dans ce groupe d'âge⁴⁰ sont très rares. Cependant, la littérature rapporte que les enfants de 5 ans possèdent déjà des anticorps neutralisants contre les types suivants d'Adénovirus 1, 2, 5, 6.⁴¹ C'est dire qu'ils ont présenté dans leur passé des atteintes par ces virus mais qu'actuellement, on connaît très peu l'importance et l'intensité des symptômes que provoquent ces virus chez les enfants et les nourrissons. D'autre

part, les Adénovirus 4 et 7 provoqueraient des infections respiratoires plutôt chez les adultes,⁴² tandis que les Adénovirus type 8,⁴³ 9, 10 sont très peu répandus⁴⁴ car peu d'adultes présentent dans leur sérum des anticorps neutralisants vis-à-vis de ces 3 derniers. Quant au type 3, on peut conclure d'après la littérature que cet Adénovirus se rencontre avec la même fréquence chez les enfants et les adultes.⁴⁵

Il existe des variantes dans certains types d'Adénovirus. La variante la plus connue est le sous-type 7a qui semble se retrouver surtout comme cause

de pneumonie chez les enfants.⁴⁶ D'autre part au Japon, des chercheurs ont isolé une souche d'Adénovirus qui est intermédiaire entre les types Adénovirus 3 et 7.⁴⁷ Un schéma sur les autres relations antigéniques observées parmi les Adénovirus, est représenté dans la publication Uchida.⁴⁸ On y trouve les réactions croisées dites majeures ou mineures parmi les différents sérotypes.

Dans un prochain travail nous nous proposons de continuer cette étude des virus dans les infections des voies respiratoires en rapportant nos résultats personnels.

GENERAL PRACTICE

THE PLACE OF TRANQUILLIZER AND ANTIDEPRESSANT DRUGS IN PRACTICE*

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A HEALTHY controversy continues to be manifested in the field of psychiatry concerning the use of drug therapy. This controversy is related to the following factors: (a) the complexity of new drugs and the multiplicity of drugs offered from month to month to the physician. (b) The difficulty in determining the effect of the drug as distinct from the psychological influence of placebo administration. (c) The pressure on the physician for medication trials due to the distress of the patient and his need for a dramatic therapeutic procedure.

The drugs which will be considered in this paper are the tranquillizers and the antidepressants. A tranquillizer may be thought of as a drug effecting reduction of anxiety with minimal disturbance of concentration and memory. The drug acts primarily on the reticular structure of the brain stem and midbrain area, as compared with the sedative that has mainly a cortical site of action. The advantage of the tranquillizer is that it relieves anxiety and tension without disturbing high-level thought processes. Consequently it is useful for the ambulant patient who remains at work, and is of value in his psychotherapeutic treatment.

The antidepressants are specific drugs designed to counteract depression and have little effect on anxiety. They constitute a considerable advance in psychiatry, have reduced the use of electroshock treatment, and have facilitated the treatment of some depressive states on an office-patient basis. They have also prevented the recurrence of depression after successful treatment in hospital.

PRINCIPLES INVOLVED IN DRUG MANAGEMENT

It is necessary to have an adequate knowledge of the patient's psychiatric background and physical health before determining the use of medication. It is to be remembered that a drug does not substitute for the doctor-patient relationship. Familiarity with the action, side effects and toxicity of any new drug in this field should be firmly established before it is prescribed, and the physician should change only with caution to a new drug offered in this area. The cost of drugs remains an important factor in their choice, as therapy may involve several months of medication. The author's impression of the usefulness of these drugs is based on experience in the field of private practice in psychiatry and will differ somewhat from the indications applicable in a mental hospital setting.

The tranquillizers are mainly differentiated in three groups: (1) the rauwolfia alkaloids, (2) the phenothiazine derivatives, and (3) a miscellaneous group such as meprobamate and hydroxyzine hydrochloride.

RAUWOLFIA ALKALOIDS

The rauwolfia alkaloids have been advocated for their tranquillizing effects and were the subject of research studies initiated in 1947. The alkaloid utilized for this purpose is reserpine. In 1950 clinical trials showed that this drug possessed a tranquillizing effect. It was also found to produce lowering of blood pressure and slowing of heart rate. It was consequently used in a wide range of psychiatric conditions, but in some cases precipitated acute depression and reactivation of psychotic symptoms. The unpredictability of its effects has made it a difficult drug to use in psychiatric practice outside the mental hospital.

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PHENOTHIAZINE DERIVATIVES

The phenothiazine derivatives include a considerable number of drugs, some of which are promethazine (Phenergan), chlorpromazine (Largactil), promazine (Sparine), thioridazine hydrochloride (Mellaril), trifluoperazine (Stelazine), perphenazine (Trilafon), and levomepromazine (Nozinan).

Promethazine was initially used as an antihistaminic and was found to have tranquillizing effects. This led to the study of related compounds, principally chlorpromazine. This drug rapidly found a wide range of usefulness in the medical fields of anesthesia, surgery, obstetrics, gynecology and psychiatry. Chlorpromazine was first synthesized in France in 1950 and introduced clinically in this country in 1954. In addition to its effects as a tranquillizer, it has an antiemetic action, as well as a potentiating influence on the effects of barbiturates and alcohol. Cardiovascular changes, particularly hypotension and tachycardia, were observed in association with this drug. It was soon recognized that chlorpromazine produced marked reduction of anxiety and was especially useful in states of excitement as found in the manic psychoses and acute delirium. In addition, chlorpromazine was found to be of value in schizophrenia, rendering the patient better able to manage the stresses of everyday living. It improved the treatment situation in mental hospitals, rendering patients more accessible to psychotherapy and other methods of treatment. The indications for the other phenothiazine derivatives are much the same as those outlined for the use of chlorpromazine. There is, however, a considerable difference in dosage range for patients in the ambulant group. The following doses are recommended for the various drugs in this group:

Chlorpromazine 25-50 mg. four times daily

Promazine 50-100 mg. four times daily

Thioridazine 10-25 mg. thrice daily

Trifluoperazine 2-4 mg. thrice daily

Perphenazine 4-8 mg. thrice daily

Their side effects include tachycardia, accommodation disturbances, hypotension and drowsiness. The more serious side effects, such as parkinsonism, occur at high dosage levels, particularly in association with the drugs trifluoperazine and perphenazine. These, however, can be controlled by reduction of dosage or by the use of Cogentin. The serious toxic effects, agranulocytosis, jaundice and skin rashes, are related to sensitivity of the patient to the drug. The jaundice apparently occurs on the basis of obstruction of the bile canaliculi, with no effect on the liver parenchyma. The condition is reversible, usually in two or three weeks after cessation of drug therapy. It does not preclude the use of chlorpromazine, although this complication may be a source of worry to some physicians. The total experience is that this group of drugs is essentially safe under clinical supervision.

MISCELLANEOUS GROUP

The drugs in the miscellaneous group which are most widely used are meprobamate and Librium.

Meprobamate is marketed under the trade names of Equanil, Miltown and Tranquiline. It has presented minimal toxic effects but has been misused by many people prone to drug addiction. The drug is essentially an effective medication for anxiety reactions but should be avoided, or at least used with considerable caution, in individuals with character disorders, alcoholism or previous drug addiction.

A new tranquillizer, unrelated chemically to any of the other drugs, is Librium. It would seem that this drug will be of value in anxiety states, neurotic depressions and obsessive-compulsive neuroses. The side effects are minimal, mainly in the form of drowsiness and ataxia which can be handled by lowering the dosage. These side effects are more likely to occur in elderly and debilitated patients and require caution in initial medication levels. The effect of Librium is the reduction of anxiety and tension; and in some cases stimulation may occur. Many patients have reported improved appetite and weight gain on this drug.

ANTIDEPRESSANTS

There are many drugs available for use in the treatment of neurotic depression and fatigue states. Traditionally, the amphetamines such as Dexedrine and Benzedrine have been effective for this type of depression, mainly by producing euphoria and increased psychomotor activity. They are of little value in the more serious depressive illnesses. Side effects of tremor, palpitations and poor appetite occur. Methylphenidylacetate (Ritalin) is a most useful drug for the mild to moderate depressions and can be administered safely to the elderly patient and to patients with serious medical disabilities such as coronary artery disease. The side effects are minimal. Deanol (Deanor) is another drug without appreciable toxic effects which is of value in the neurotic depressions. Librium also shows considerable promise in its effect on depression.

For the psychotic depression, two groups of drugs are used: the amine oxidase inhibitors and imipramine (Tofranil). Iproniazid (Marsilid) was the first of the amine oxidase inhibitors to be introduced. This is an inhibitor of the enzyme monoamine oxidase. The resultant effect is an increase in brain serotonin which may affect neurohormonal control at the synapse. Iproniazid was found to be effective in psychotic depressions that had not responded to electroshock treatment and was considered to facilitate recovery in these depressions in conjunction with other methods of treatment. Serious toxic effects were reported, mainly in the form of liver cell damage and, in some cases, acute hepatic necrosis. It is felt, however, that

these toxic effects were due to excessive dosage. The drug has subsequently been considered reasonably safe in lower dosage levels with close clinical supervision. Similar drugs of less toxicity have been marketed, namely, phenylzine dihydrogen sulfate (Nardil) and nialamide (Niamid). Their indication and method of action are similar to those of iproniazid. Side effects of vertigo, dry mouth, perspiration, ankle edema and hypotension have been reported. Dosage levels in this group should be reduced to maintenance levels after two to three weeks with adequate medical supervision. In summary, the indications for the amine oxidase inhibitors are as follows:

- (1) For the treatment of low-grade depression not requiring hospitalization and without suicidal risk.
- (2) For the management of serious depression in hospital, usually in conjunction with electroconvulsive therapy.

Imipramine (Tofranil) is the other drug to be considered in this antidepressant group. It is closely related chemically to the phenothiazine group but has no action as a tranquillizer and is not an amine oxidase inhibitor. It does, however, increase the level of brain serotonin and has some action on the central nervous system function at the synapse. Its side effects include dryness of mouth, blurring of vision, hypotension, tachycardia, and with high dosage, urinary retention. In view of the hypotensive effect, it should be used with caution in elderly persons and patients with cardiac failure or coronary heart disease. Dosage levels of 25 mg. four times daily are adequate and it is doubtful if higher levels are of value. After recovery from the depression, maintenance treatment with 25 mg. daily should be carried on for one or more months.

Experience indicates that the more serious depressions will not respond to drug management within a short time and that hospitalization is advisable to protect the patient from suicide and to provide adequate care. Electroshock treatment is indicated in conjunction with drugs in this group for the severe depressions with suicidal drives and for the group of patients who do not respond satisfactorily after an adequate trial with medication alone.

PSYCHIATRIC PROBLEMS IN CHILDREN

Tranquillizers have been used to a moderate degree in the treatment of similar psychiatric conditions in children, as in the anxiety reactions and the associated somatic symptoms. They are also of value in childhood schizophrenia. Promethazine has been a particularly helpful drug with very minimal side effects. Promazine and thioridazine have proved to have a similar function. Children who have such problems as speech defects, enuresis, sleepwalking, and nightmares may be helped by several months of therapy with these medications. Deanol

has been recommended for behaviour disorders, as have drugs of the amphetamine group, such as dextro-amphetamine. Caution should be exercised in the use of the more recently developed phenothiazines of higher potency, as a syndrome suggesting brain tumour, encephalitis, meningitis, and tetanus has been noted in children in association with their administration.

In conclusion, it may be stated that the advent of the tranquillizer drugs represents a considerable advance in the treatment of psychiatric patients, particularly those with a psychosis. Antidepressant drugs have improved the management of depressions and decreased the need for electroshock treatment, although this treatment is still indicated for patients who have severe depressions with suicidal drives. These drugs have decreased significantly the length of hospital stay, permitting improved rehabilitation of the patient within his community.

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DIET AND THE RHEUMATIC DISEASES

No mode of treatment of various kinds of arthritis has been so falsely exploited as that of diet. A little of this is due to the experimental difficulties of getting scientifically valid answers in so complex a problem in so unreliable a species as man. More, however, is likely due to some more basic appeal to the patient's psychology. A special diet program may appeal as a way of getting rid of the consequences of some wrong-doing by the traditional method of partial fasting, or because it costs little effort to give it a try and the situation seems desperate. The scientific absurdity of the recent fad to "lubricate the joints" by taking oily foods according to a rigid schedule need not be elaborated; although perhaps it is worth noting that joints are lubricated (with extraordinary efficiency) by mucinous materials built out of simple sugars available from all foods; and not by oily, fatty, or cholesterol-containing foods. Yet this patently absurd fad has recently scored a remarkable financial success.

It has been well established that none of the common rheumatic diseases can be ascribed to a deficiency of calories, fat, carbohydrates, protein, or any of the many presently known vitamins or nutritionally important minerals. Excess amounts of any of these substances are without therapeutic value; this includes foodstuffs in pure form such as vitamin C, or as lemon juice, gelatin, sassafras seeds, etc. Obviously a well-balanced diet is to be advised to maintain the best possible general health, but not for any specific therapeutic value.

"The arthritic patient still wants a special diet, the disease usually does not need one." This statement is true for all of the common rheumatic diseases with the probable exception of gout.—C.A.R. Scope, September 1960.

CASE REPORTS

BASAL CELL CARCINOMA OCCURRING IN BURN SCARS

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IT IS WELL known that epidermoid carcinoma may occur in scars. It was known long before Marjolin¹ wrote his classical paper on the subject. It is perhaps less well known that basal cell carcinoma may occur under these circumstances. The following case, while unusual, will illustrate the necessity of dealing promptly with scars which appear active or are a source of complaint to the patient.

In 1949, R.S., a 45-year-old smelter worker, was burned on the anterior chest by some molten metal. This resulted in a triangular-shaped scar of about 1½" at its widest point. It was quiescent until 1954. At that time he complained of tenderness in one margin of the scar. He was seen by his physician, who noted some induration and a scaly surface at the site of

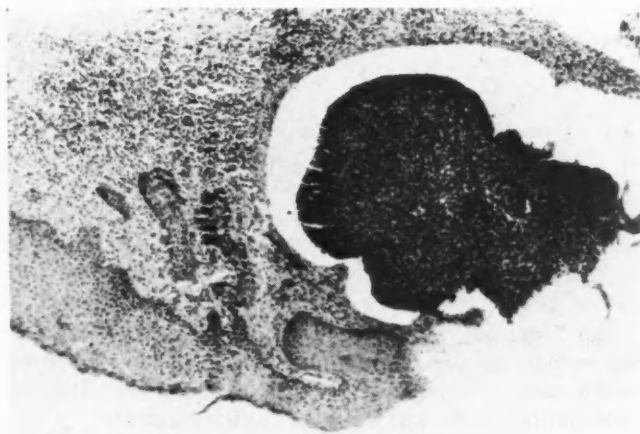


Fig. 1

tenderness. He was seen on several occasions over the next two years with some increase in the size of the scar. In 1956 the scar was widely excised and the defect closed with an intermediate split skin graft. The tissue examination (Figs. 1 and 2) revealed a typical basal cell carcinoma in the margin of the scar.

In 1957 the patient was burned on the forehead by the same material. The burn resulted in a small scar approximately ½" in diameter. He was seen six months after the original injury. At this time his complaint was that the scar "wasn't healing properly". On examination he was noted to have a reddened scar with a scaly surface. It was freely movable; there was no evidence of ulceration and no enlargement of the regional lymph glands. The abnormal tissue was widely excised and the defect closed. The pathological examination revealed a basal cell carcinoma of the scar (Figs. 3 and 4).

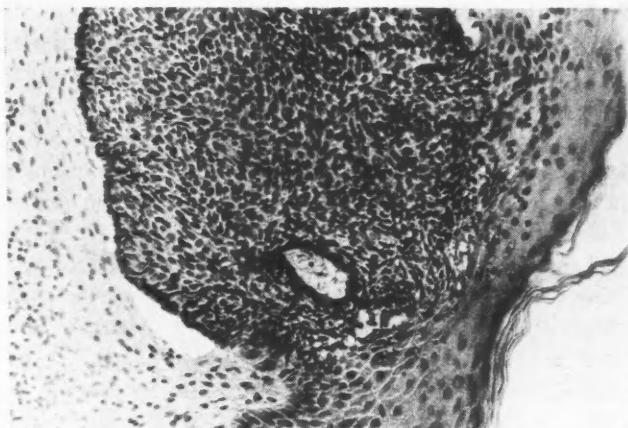


Fig. 2

DISCUSSION

Classically, basal cell carcinoma is a disease of the fifth and sixth decades, and in 95% of the cases the tumour occurs in the head and neck region.² The etiological factors are principally actinic and



Fig. 3

ionizing radiation. Occasionally chemicals and petroleum products can produce this tumour. Mechanical injury is not considered to be an etiological factor. The tumour is commoner in younger people



Fig. 4

than is generally realized and it is found in more people under 60 years of age than is epidermoid carcinoma.³ Basal cell carcinoma has no characteristic gross appearance, and in 37% of the cases there is a history of a presumably benign pre-existing lesion.⁴ These factors probably account for the long delay in establishing tissue diagnosis which is evident in the literature.⁵

The exact relationship of skin cancer to scars is not easy to establish. Of 60 tumours occurring on the leg, arm, scalp and trunk, 18% were in scars, whereas in other sites only 0.77% were in scars. In their series of 1374 cases of basal cell carcinoma, Treves and Pack⁷ found only seven instances in which the tumour was in burn scars. Murray and Cannon⁵ found six cases in their series of 42 patients where basal cell carcinoma occurred in scars, two of which were burn scars. Webster⁸ mentions a case in which the carcinoma developed in a burn scar after a superficial scratch. The author knows of two instances where basal cell carcinoma occurred in scars, one after thermal injury to the eyelid and the other after a dog bite on the dorsum of the hand.

The mechanism of carcinogenesis in these circumstances is not well understood. It is felt that

diminished blood supply and atrophy of the adnexa and epidermis may play a part. Possibly this renders the tissues more sensitive to the damaging effects of actinic radiation, since most of these tumours are associated with chronic solar dermatosis. The scars may show keratosis or fissuring before carcinoma develops. The presence of carcinoma may be indicated by an induration, an ulceration or a raised plaque.

SUMMARY

A case of basal cell carcinoma in burn scars is reported. A brief review of the literature is presented.

I would like to thank Dr. J. B. McKay, Provincial Pathologist, Toronto, for the preparation of the photomicrographs.

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PERINEAL RECONSTRUCTION AFTER VULVECTOMY*

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LEUKOPLAKIA VULVAE is well recognized as a precancerous lesion.* The disease affects mainly the older age group, but occasionally younger women are afflicted by the condition. The accepted treatment today is vulvectomy. Many excellent papers on this subject have appeared in the recent literature, but few of the authors discuss early or late postoperative morbidity associated with the procedure.

Collins *et al.*¹ state that in 11 of 41 cases of simple vulvectomy there was slight breakdown of the wound postoperatively. Six of 40 patients followed up required further minor procedures, consisting of excision of a painful scar or fold.

Green, Ulfelder and Meigs² state that split skin grafting, immediate or delayed, is occasionally used with radical vulvectomy, and that minor degrees of wound infection and marginal necrosis of skin flaps were encountered in nearly one-half of the 238 cases reviewed.

The following case is an example of the late morbidity associated with partial vulvectomy.

A married white female, aged 55, was admitted to St. Michael's Hospital in January 1959. She stated that in 1947 she had undergone partial vulvectomy for leukoplakia, and that in 1948 she had had further excision of leukoplakia vulvae with split skin grafting to the area. Since that time she had been well, except for symptoms related to the perineum.

She had had intermittent cracking and redness of the vulvar area, accompanied by a chronic anterior fissure-in-ano. Treatment at various times consisted of local ointments, saline baths and vinegar baths.

Sexual intercourse had been impossible for several years. Recently, the act of walking had caused a stretching of the perineal area, further aggravating her symptoms.

General physical examination was negative. Perineal examination showed no evidence of leukoplakia but there was marked scarring of the area. Abduction of the thighs was greatly limited. There were tight bands running transversely anterior and posterior to the introitus, and the anterior margin of the anus was fixed to the introitus by scar tissue. The urethral orifice and distal one-third of the urethra were intimately involved with scar tissue, the urethra being pulled anteriorly. The introitus admitted the tip of the small finger (Fig. 1a).

An operation was performed on February 8, 1960, under general anesthesia with nasotracheal intubation, the patient being placed in the lithotomy position. After skin preparation and draping, a vertical incision was made in the midline from the area of the clitoris to the urethra. The clitoral stump was dissected free from the surrounding scar, and transverse incisions

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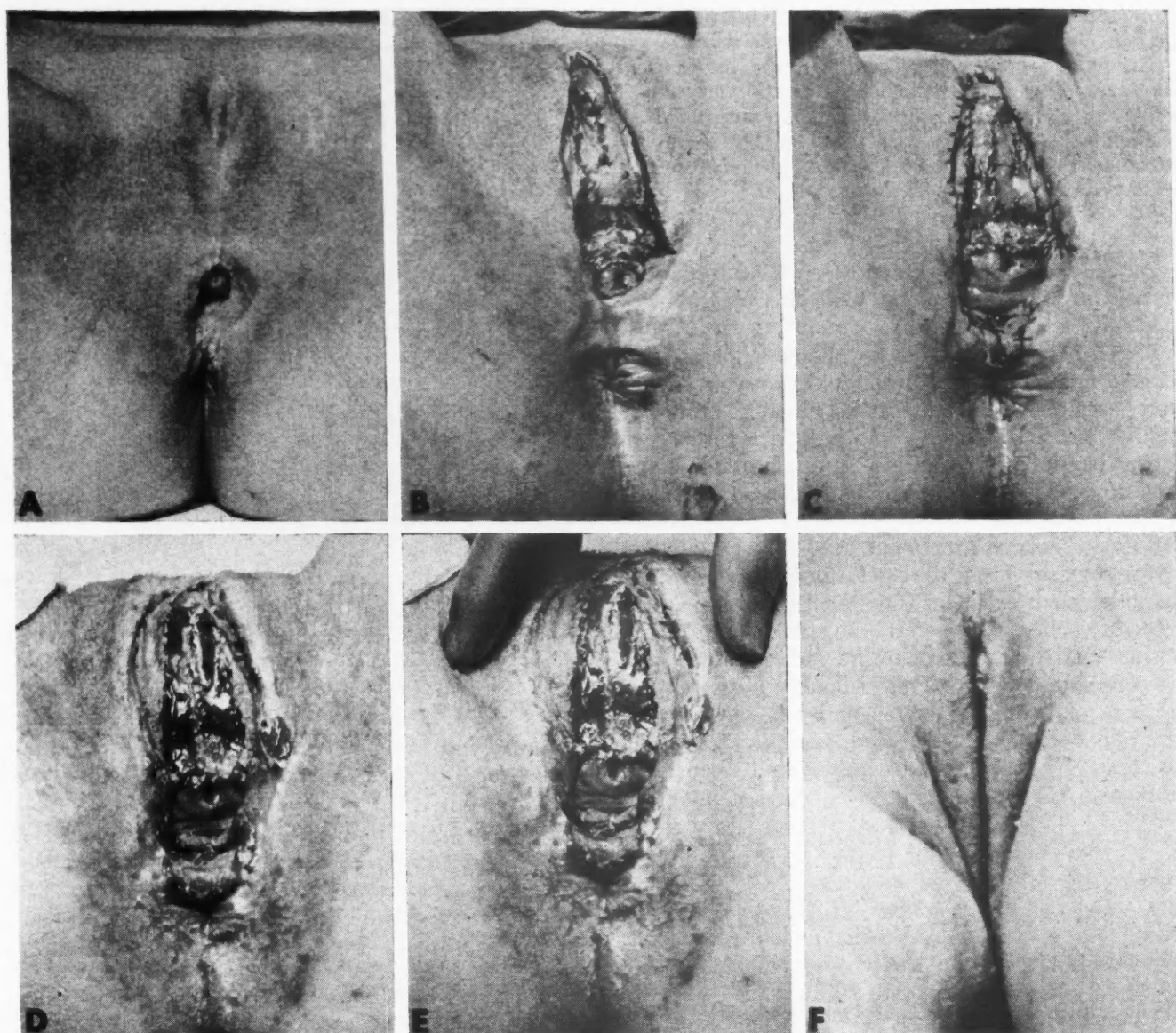


Fig. 1.—A Preoperative appearance of vulva. B Upper portion of original defect recreated. C Mucous membrane and split skin grafts sutured in position. D, E, F, Appearance of perineum one week after operation; labia satisfactorily protect introitus.

were made extending laterally from the urethral orifice (Fig. 1b). A second vertical incision was then made from the posterior border of the vagina to approximately 0.4 cm. inside the anal verge. This allowed the skin to fall to either side, producing the original defect from the vulvectomy. Excision of all scar tissue in the area was carried out, replacing the posterior perineal region and the anus to a relatively normal anatomical position, and setting back the urethral orifice and the distal third of the urethra.

Full thickness mucosal grafts were excised from the lower buccal sulcus bilaterally. These grafts measured approximately 1.3 cm. by 5.0 cm. The defects created in the mouth were closed by advancement and direct suture. A split skin graft approximately 12/1000" in thickness was removed from the right thigh. The donor area was dressed with gauze impregnated with Scarlet Red.

The free mucosal grafts were placed in the midline of the defect which had been created, extending from the clitoris to the urethra, and enclosing the stump of the clitoris. The split skin grafts were placed on either side of these, creating large labia majora. A split skin graft was placed in the diamond-shaped defect created

between the posterior walls of the vagina and anus. All grafts were affixed in place using black silk sutures at the margins and through and through "quilting" type sutures in the grafts (Fig. 1c). A firm tie-over dressing consisting of absorbent cotton impregnated with paraffin and sulfathiazole crystals was affixed to the operative areas and a No. 16 French Foley catheter was inserted into the bladder.

Postoperatively, the patient was given a low-residue diet and erythromycin, 250 mg. six-hourly for seven days. Her postoperative course was uneventful. The patient was taken to the operating room again on February 15, 1960. Under general anesthesia the dressings were removed and all the grafts were found to be satisfactory (Figs. 1d and 1e). The reconstructed labia protected the introitus (Fig. 1f). The catheter was removed. Again, her postoperative course was uneventful and the patient was discharged from hospital on February 22, 1960. At this time the donor sites in the buccal mucosa and right thigh were healed.

The patient was examined four months after operation. She stated that she had had no symptoms referable to the genitalia since operation. Intercourse was possible, without difficulty, four weeks after operation.

No symptoms of cracking, redness, or pulling in the perineal area were elicited. Walking was unrestricted.

Examination revealed all grafts to be in excellent condition. The mucous membrane grafts were almost indistinguishable from normal vaginal mucosa. Free abduction of the thighs was possible. There was an adequate introitus, and no tension on either the urethral orifice or the anus (Fig. 2).

CONCLUSIONS

Partial vulvectomy evidently cured this patient of her original disease, but the late contractures made her a semi-invalid.

Modern surgery should be planned not only to remove completely the original disease but to restore normal function as far as possible. It is not enough to excise tissue and "pull it together" or allow the defect created to "granulate in", since this invites such problems as secondary wound healing, and later, fibrosis, leading to contractures and loss of normal function.

It is suggested that the operation outlined, which has given such excellent functional results as a late procedure, be planned at the time of primary closure, and that the repair be incorporated with the original operation. This is doubly important in the case of younger women, and will obviate the possibility of excising diseased tissue inadequately for fear of residual scarring and its ensuing problems.



Fig. 2.—Appearance of vulva four months after perineal reconstruction.

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SHORT COMMUNICATION

EVALUATION OF INTRAVENOUS HUMAN FIBRINOLYSIN AS A TREATMENT FOR RECENT INTRAVASCULAR THROMBOSIS*

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THROMBOTIC OCCLUSION of a vessel is a dynamic process. A thrombus is built up by the deposition of successive layers of platelets and fibrin. This process is opposed by the natural fibrinolytic activity of the blood. The size of a thrombus will increase if platelets and fibrin are deposited more rapidly than they can be removed. For this reason, any measures that will increase the fibrinolytic activity of the blood may be expected to be of value in the treatment of recent thrombosis.

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Plasminogen, a normal component of plasma, can be activated to form plasmin, a proteolytic enzyme capable of dissolving fibrin. Activators of plasminogen are found in many different tissues and are also produced by bacteria.

This report concerns the administration of Actase,* a material said to contain plasmin. Actase is prepared from a human plasma fraction containing plasminogen. This is activated by the addition of purified streptokinase.

METHOD AND OBSERVATIONS

The material was given to 10 patients with recent thrombosis in arteries or veins. The usual dose was 50,000 units per infusion. This was given in 200 c.c. of normal saline over a period of one hour. Five of the patients received more than one infusion. The results of treatment are summarized in Table I.

There was no objective evidence of improvement in any of the cases. Pyrogenic reactions occurred

*Actase Fibrinolysin (Human) supplied by the Ortho Pharmaceutical Corporation, Raritan, New Jersey.

No.	Diagnosis	Dose	Febrile reactions	Remarks
1	Thrombosis of R. axillary vein	10,000 units	Nil	Infusion into the involved arm stopped after only 10,000 units because of pain in the arm. No improvement
2	Thrombosis of R. femoral artery graft	50,000 units	Nil	No improvement.
3	Traumatic rupture of R. popliteal artery. Grafted.	65,000 units	Yes—105° F.	Chills and fever. Mild jaundice the day after infusion. No improvement. Leg amputated.
4	Septic thrombophlebitis of orbital veins	175,000 units	Nil	No improvement.
5	Thrombosis of L. femoral artery	45,000 units	Yes—103.6° F.	No improvement.
6	Thrombosis of aortic graft	100,000 units	Yes—102° F.	No improvement. Patient died of mesenteric artery occlusion with infarction of the bowel.
7	Buerger's disease, gangrene of toes	50,000 units	Yes—103° F.	No improvement. Severe reaction—see text.
8	Mesenteric thrombosis	50,000 units	Yes—104° F.	No improvement. Subsequently developed thrombophlebitis in the arm used for the infusion.
9	Thrombophlebitis L. leg	100,000 units	Yes—100.8° F.	No alteration in the natural course of the disease.
10	Retinal vein thrombosis	100,000 units	Yes—104° F.	No improvement.

in seven. In one case, the patient with Buerger's disease, a violent reaction occurred with vomiting, peripheral vascular collapse and an increase in the area of ischemia in his leg.

Because of this unfavourable clinical experience the activity of the material was questioned. *In vitro* testing was then carried out on fibrin plates. Some of these consisted of bovine fibrin clot containing human plasminogen. They were sensitive to plasminogen activators as well as plasmin. When such plates were heated to 70° C. for 60 minutes, the human plasminogen was destroyed and the plate could then be used to test for plasmin alone. Filter paper discs were dipped in the solution to be tested and then placed on the fibrin plate. After incubation at 37° C. for 12 hours the clear zone of fibrinolysis was observed. Urine, which contains the activator urokinase, was used as a control.

The material was tested in two strengths. The recommended dosage intravenously was 50,000 units in 200 c.c. or 250 units/c.c. Repeated testing from different lots of Actase Fibrinolysin (Human) at this strength revealed no activator or fibrinolytic activity. It was then tested at a strength of 2500 units/c.c. On one occasion this showed activator activity comparable to that of normal urine. However, at no time could any fibrinolytic activity be demonstrated.

DISCUSSION

In contrast to the experience reported at the Symposium on Clinical Effects of Fibrinolytic Activity,¹ Actase Fibrinolysin (Human) has not proved a useful therapeutic agent in this small group of patients. Similar doubt of its effectiveness has been expressed recently by Fletcher *et al.*²

It is difficult to understand why a material said to contain active fibrinolysin is unable to dissolve fibrin *in vitro*. Its effectiveness in dissolving thrombus *in vivo* must be seriously questioned.

SUMMARY

In 10 patients the intravenous administration of Actase Fibrinolysin (Human) did not prove effective in the treatment of recent intravascular thrombosis. Pyrogenic reactions occurred in seven of these patients. *In vitro* testing failed to demonstrate the presence of active fibrinolysin.

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TREATMENT of the child with acute rheumatic fever and probable heart disease should include the administration of steroids and salicylates, preferably a combination of the two. Duration of treatment must depend on evidence of inactivation of the infection and on improvement of the patient's over-all condition. Physicians must also consider the use of penicillin—which, according to recent information, "may be far more crucial in the treatment of acute rheumatic fever than either salicylates or steroids, or both." Bed rest should also be part of treatment, but at some judiciously timed point or points ambulation should be recommended while chemotherapy continues to be administered.—H. M., guest editorial (*Canad. M. A. J.*, 83: 823, October 8, 1960). —"Editorial Capsules" in *Medical Tribune*, November 7, 1960.

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(Information regarding contributions and advertising will be found on the second page following the reading material.)

THE ENIGMA OF BENIGN FIBROBLASTIC
HYPERPLASIA

RECENTLY, attention has been re-focused on a bizarre and uncommon disorder designated as idiopathic retroperitoneal fibrosis.¹⁻³ The first clear description of this disorder was apparently recorded in 1948 by Ormond,⁴ although earlier reports contain references to individual cases with features suggesting that they represented basically the same lesion. Idiopathic retroperitoneal fibrosis is a histologically benign, self-limited, fibroblastic hyperplasia and proliferation that results in an insidious, progressive fibrosis of retroperitoneal connective tissue. Here, "in this hinterland of straggling mesenchyme with its vascular and nervous plexuses, its weird embryonic rests and its shadowy fascial boundaries"⁵ a creeping mat of fibrous tissue begins to take form in the fascia surrounding the bifurcation of the great vessels about mid-lumbar level, spreads distally to the vicinity of bifurcation of the iliac vessels and laterally between the limiting layers of the retroperitoneal fascia. As it extends inexorably, the fibrous tissue mass surrounds the aorta and vena cava, the para-aortic lymph nodes, the lymphatic vessels, and the ureters. The end result is usually the compromise of both ureters, though sometimes only one may be affected, with impairment of transport of urine between kidney and bladder, hydroureter, hydronephrosis and gradual failure of renal function.

This disorder affects males twice as commonly as females and occurs most frequently in the fifth and sixth decades of life. To date no satisfactory explanation of the etiology of this strange malady has been forthcoming. It does not satisfy the usual criteria of malignancy. Despite the extent of the spreading fibrosis, it does not invade structures such as the ureters, blood vessels, viscera or the posterior peritoneum, although it may be adherent to the latter. Secondary lymph node enlargement is not a feature. There is no evidence of metastasis. In the cases reported, no antecedent inflammatory

or other lesion could be elicited to explain the connective tissue sclerosis. Whatever its nature, this process appears to be a self-limiting one. It seems highly probable that this disorder represents the same basic process as that which has been variously described as periureteritis plastica, pericystitis plastica, and perirenal fasciitis.

The simplicity of the microscopic pathological features only serves to magnify the mystery of their underlying nature. The fibrous tissue is composed of bundles of collagen, of variable density and hyalinization depending upon its age, sometimes arranged in whorls, with typical fibroblasts scattered throughout the mass. If the lesion is in its earlier stages of development, it contains large numbers of actively proliferating young fibroblasts; as it matures, the fibroblasts become smaller and less numerous and the collagenous bundles more voluminous and densely packed. Areas of fatty tissue, infiltration by mononuclear cells, eosinophils and some neutrophils, and perivascular round cell collections have been noted in some cases. The fibrous connective tissue surrounds but does not invade the blood and lymph vessels, lymph nodes, nerves and ureters. Its marginal zone may show a rather sharp line of demarcation from the surrounding tissues but no evidence of encapsulation has been observed. This microscopic appearance has been likened to that of a keloid.

Clinically, the early stage of this disorder is vague and insidious, its symptoms are variable and inconstant, and physical signs are frequently absent. Obscure pain is a common and distressing early complaint, in the form of low backache, lumbar or costovertebral aching, or pain in the flank, lateral abdomen, or in the lower abdominal quadrants or inguinal regions sometimes radiating to the inner aspect of the thigh or testicle. "Retroperitoneal pain can be severe and persistent enough to drive the most phlegmatic patient to distraction, but where there are no physical findings, his complaint is likely to be received with incredulity."⁶ At times the "pendulum character" of the pain may be a helpful diagnostic feature. Because it is essentially caused by pressure or traction on relatively fixed and highly sensitive structures, it is strongly influenced by gravity. Commonly the patient prefers to lie face down or buckled over the edge of the bed. The pattern of these contortions changes as the lesion extends and expands, and they do not usually afford as much relief as they do to a patient with diaphragmatic hernia or a high gastric ulcer.

Other variable complaints include attacks of nausea and vomiting, anorexia, weight loss, asthenia, pyuria, urinary frequency, oliguria and finally anuria and renal failure with its distressing associated manifestations. Anuria, signifying complete obstruction (functional or organic) of both ureters, is the most significant and one of the most common presenting manifestations.

Physical examination may show few or no abnormal signs. Occasionally, tenderness in the costovertebral angles, flanks or abdomen, or a palpable mass in the loin or abdomen may be present. Significant temperature elevation is uncommon. The urine is normal in the majority of cases, though pyuria, hematuria and albuminuria have been observed in some. Moderate anemia and slight leukocytosis are common and nitrogen retention is the usual accompaniment of the late stages of renal failure.

The ureter is usually the last structure to be enveloped by the proliferating fibrous tissue, but when involved it invariably gives rise to symptoms. Gradual ureteral obstruction leads to increasing hydronephrosis and hydronephrosis, frequently complicated by infection, with pyonephrosis and pyelonephritis eventuating in renal destruction, and, if bilateral, renal functional failure and uremia. Ureteral obstruction may occur suddenly and result in anuria before any damage to the renal pelvis or kidney has occurred. In such cases, relief of the ureteral obstruction may lead to recovery without permanent renal damage. That ureteral obstruction is not necessarily due to strangulation of the ureter by the surrounding fibrous tissue with resulting occlusion of the ureteral lumen is evidenced by the observation that in some patients with complete anuria, ureteral catheters can be passed freely and pyelography shows no evidence of ureteral block. In such cases it has been suggested that the block is a functional or physiological one, due to the inhibition of ureteral peristalsis by the encasing fibrous tissue sheath.⁶

Radiographic studies, at least in the early stages of this disorder, mislead as often as they clarify. Gastric series and barium enemas show no abnormality or, worse, may "provide the clinician with a wide choice of red herrings".⁵ Intravenous pyelograms, ureteral catheterization and retrograde urography are, of course, essential forms of investigation and may or may not reveal narrowing or obliteration of the mid-portion of one or both ureters and dilatation of the proximal ureters and renal pelves. A helpful urographic sign which is sometimes present is a medial deviation or kink, sometimes approaching a 90° angle, in the mid-portion of the ureter where the constriction of its lumen may be noted, as though the fibrous tissue medial to one or both ureters had undergone shrinkage and contracture after its initial phase of active proliferation. Unfortunately, aside from the finding of medial deviation of the ureters, these abnormal urographic changes do not throw any light on the nature of the lesion responsible for them. Presacral carbon dioxide insufflation could conceivably be of value in obscure cases, but the mortality from this procedure is higher than that of an uncomplicated laparotomy and under these circumstances it seems seldom if ever justified.

In most cases, the final diagnosis is made at operation or autopsy. Biopsies should be deep, well-

placed, generous and taken from more than one area,¹ but even this procedure is not without its diagnostic pitfalls and it should be properly regarded as just one additional, helpful diagnostic technique, neither more nor less valuable than the information revealed by a searching history and the use of the unaided basic senses.

To characterize this mysterious phenomenon of retroperitoneal benign fibroblastic proliferation of unknown etiology as an enigma is to emphasize the obvious. It is of interest, and possibly of value in pointing to avenues for future investigation, to speculate on the fundamental relationship between this unusual malady and other lesions with a basically similar pathological foundation. The pathological counterpart of this disorder involving the connective tissues of the mediastinum, for example, has recently been described and one case at least has been reported in which diffuse, progressive fibrosis of similar type involved both retroperitoneal and mediastinal sites.⁷ Proceeding further in this area of speculation, it could be pointed out that essentially the same basic histopathological changes, pursuing a comparable natural course insofar as the evolution of microscopic features is concerned, are to be observed in such diverse forms of connective tissue fibroplasia as keloids, Dupuytren's contracture, dorsal knuckle pads, fibromatosis of the plantar fascia, and Peyronie's disease.

It would seem desirable that specific search for each of these far-flung manifestations of connective tissue fibromatosis should be made and recorded when any one of them is encountered.

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THE PATHOGENICITY OF CANDIDA TROPICALIS

OF the more than 30 species of the genus *Candida*, only *C. albicans* has heretofore been considered potentially pathogenic to man. Of late, however, there has been an increasing body of evidence indicating that under certain circumstances *Candida tropicalis* may also produce clinical disease in humans, at times with fatal results.

Additional evidence of the pathogenic capabilities of this organism is supplied in a recent report by Richart and Dammin of two fatal cases of septicemia due to *C. tropicalis* (*New England J. Med.*, 263: 474, 1960). One of these patients, a 65-year-old woman with pneumococcal otitis media and meningitis, died despite intensive treatment with penicillin. Antemortem blood cultures were positive for *C. tropicalis*. Necropsy revealed the presence of focal areas of encephalitis, adrenal medullary hemorrhages, a profuse growth of *C. tropicalis* in the adrenal cortices and a remarkable invasion of

the bladder wall by this organism. The second patient, a 57-year-old woman, admitted to hospital because of prolonged anuria, also succumbed, and at necropsy presented pathological and cultural evidence of *C. tropicalis* septicemia.

In several of the cases reported, *Candida* infection followed the administration of large doses of antibiotics. In this regard it is noteworthy that, *in vitro*, tetracyclines appear to exert a direct growth-potentiating effect on *C. albicans*, and that the administration of penicillin is associated with an increased mortality of embryonic chicks infected with *C. stellatoidea*.

The knowledge that yeasts such as *C. tropicalis*, hitherto relegated to the role of harmless saprophytes, may assume virulent pathogenicity, particularly after alteration of the flora of other organisms through the agency of antibiotics which are in such widespread use, is cause for some concern. *C. tropicalis* has been found to be present with relative frequency in the sputum of many patients with chronic bronchitis, and it is evident that the demonstration of this organism warrants more consideration than it has received in the past.

H.O.D.

CAVEAT EMPTOR

A MEMBER has recently outlined his experience in answering one of the classified advertisements in the Journal. He was interested in a hospital appointment in the United States, and correspondence with an advertiser confirmed the attractiveness of the post in question, so much so that he had taken several steps towards relinquishing his practice. At a very late stage in the proceedings, he became aware that state board licensure and American citizenship were required and he was not qualified in either respect. His reaction was one of resentment that the Association had not protected his interests by demanding of the advertiser that such essential information be stated in the text of the advertisement.

It is admittedly a duty of responsible medical publishers to determine insofar as possible that advertisements are not misleading. We are frequently consulted by the *British Medical Journal* on the *bona fides* of classified advertisements submitted by Canadian institutions and individuals, and frequently we are instrumental in having the facts stated more comprehensibly for British readers. We demand that practice opportunities be described in terms of population, number of doctors serving the area, hospital facilities, accommodation and financial arrangements. We urge box holders who desire to retain anonymity to acknowledge all correspondence, and we insist that public appointments be advertised in conformity with the scale of qualifications and remuneration established by the Canadian Public Health Association.

There is, however, a limit to the detail which can be demanded in a classified advertisement, and

one must recognize that the advertiser desires to present his proposal in its most favourable light. Ordinary prudence demands that respondents to classified advertisements satisfy themselves on the details of any offer, and the best way to accomplish this is to ask questions.

In the first letter, the respondent should briefly describe himself: his age, his marital status, his university and year of graduation, his other professional qualifications, his licensure, his experience, his nationality, his religion, his present employment and his date of availability.

He should ask for a clear outline of all financial arrangements, both in the case of a salaried appointment and in the instance where the purchase of facilities is involved. In those cases where association with another doctor or group of doctors is contemplated, the applicant should request a written contract for study. He should satisfy himself that a restrictive covenant is not part of the contract or that the terms of any covenant are such that his freedom subsequently to practise in the area is not impossible. Lastly, in respect of any new jurisdiction where a licence to practise is necessary, he should satisfy himself on his ability to meet the medical licensing requirements.

The observance of these basic precautions will prevent misunderstanding, minimize correspondence and will in many instances lead to the personal investigation without which a satisfactory conclusion is unlikely to be reached.

A.D.K.

THE USE OF A DATUM

The ways of using a published article are many. Some among our colleagues belong to the razor-blade school and cherish the papers close to their hearts by excising them, abandoning without sorrow the shredded journal that is left. The wild ones insist they "can find it when they need it," meaning the select fragments, and of course W. C. Fields used to say the very thing as he clawed through his fabulous roll-top desk. The extremely sober students write for a reprint, sometimes get it, and preserve their journals and drawerfuls of reprints as well, for which, alas, there is needed an index.

The library (when you can arrange to go there) does have several kinds of index, rather complete up to last February. The papers you have in mind were in May.

Abstracts are an attempt to circumvent these troubles, and, as a superb form of note taking, accomplish a great deal for the mind that writes them. They are less than the data, but they can retrieve the data; now it is only a question of retrieving the abstracts. All that's wanted is an index. And maybe not, for each has a title, but the information is never looked for afterward under *that* title; it is always another reason that brings the matter up.

These diverse forms of suffering come to mind because of new inventions by the chemists to make their information available. It must be splendid to work in chemistry and look up the data by clearly defined, fixed entities. By contrast, it is taxing to think in medicine, which is multi-lateral and endlessly evolving, even in its dimensions.

If an idle genius can be found, the invention wanted in medicine is a manifold and infallible index, encyclopedic and pocket-sized, that every physician can have in his desk drawer, and which guides him comprehensively to every datum he owns (or can expect to find in the library either) no matter how obliquely the occasion may evoke it. . . . The invitation is hereby extended—we will be obliged to him.—Editorial: *Medical Tribune*, November 14, 1960.

LETTER TO THE EDITOR

ELECTROCARDIOGRAPHY: PRINCIPLES AND PRACTICE

To the Editor:

I hope you can find room to print the following comment on the review of my book, "Electrocardiography: Principles and Practice", in your issue of October 29 (83: 976, 1960). Your reviewer unintentionally does me injustice when he writes, "What is one to make of a definition which says that a non-invariant [of the electrogram] is 'a characteristic which is not an invariant'?" But this definition, on page 8, is *immediately preceded* by the definition of an invariant; the quoted definition is not, therefore, absurd, as the review makes it seem, for it merely means that every characteristic which is not an invariant, according

to the preceding definition, will be called a non-invariant.

Your reviewer says that "Columns (4) and (6) in the table of misplaced limb electrodes have been interchanged." This is on page 40. The reviewer is mistaken and the columns are correct.

Your reviewer correctly says that I devote 50 pages to reciprocal excitation of the heart and conclude that it probably does not occur at all. This sounds silly, but inasmuch as this supposed arrhythmia is almost universally believed to occur, I thought it necessary to review every reported case I could find, and show that every case could be adequately explained by some other mechanism.

ERNEST B. ZEISLER, M.D.
179 East Lake Shore Drive,
Chicago 11, Illinois.

MEDICAL NEWS IN BRIEF

SURGICAL CORRECTION OF THE TETRALOGY OF FALLOT

Generally, the ventricular septal defect in the tetralogy of Fallot lies directly under the aortic ring, usually behind the so-called crista supraventricularis and anterior to the papillary muscle of the conus. Describing the various conditions that are associated with the tetralogy and which are of surgical significance, Senning, of the Karolinska Hospital, Stockholm, summarizes the results of 31 cases of primary complete correction of this anomaly and of 16 reoperations following previous shunt procedures (*Schweiz. med. Wchnschr.*, 90: 839, 1960).

Of the 31 patients subjected to primary operations, 28 had infundibular and 16 valvular pulmonary stenosis. Right to left shunt was present in all 31, and left to right shunt in nine of these patients. A prosthesis was used for closure of the septal defect in 24 cases, and for the outflow tract of the right ventricle in ten cases. Six of the patients died; four of these deaths occurred because anomalous coronary arteries were cut accidentally or right ventricular failure supervened, one died of staphylococcal septicemia and one died owing to intractable AV block. Reoperation on patients who had previously undergone a shunt operation gave most unsatisfactory results. Although only one of the first seven patients subjected to this procedure died, seven of the following nine patients succumbed. Three developed staphylococcal infection and died three weeks to three months after operation. One died following the operation because of air embolism, and three of cardiac insufficiency. In most of the patients who had primary operation, the symptoms disappeared completely, cyanosis cleared and polycythemia and clubbing of the fingers regressed within a matter of weeks. In most patients a systolic murmur persisted in the third and fourth left interspace.

The mortality associated with the use of extracorporeal circulation makes the procedure prohibitive; therefore it is recommended that operation be delayed until they reach the age of four to five years. However, in cases in which the patient's condition appears to indicate earlier operative correction, temporary amelioration by a less complete repair may be advisable.

Senning recommends that Blalock's or Pott's operations should not be employed in such palliative procedures but, if possible, valvulotomy should be performed or an anterior window placed between the ascending aorta and the main branch of the pulmonary artery.

RADIOACTIVE GOLD TREATMENT OF CARCINOMA OF THE PROSTATE

Radioactive gold (Au^{198}) was used with little success in the treatment of 42 patients with carcinoma of the prostate gland by Bulkley and O'Connor (*J. A. M. A.*, 174: 252, 1960). Experiments with dogs injected with Au^{198} , P^{32} , and Y^{90} had shown that these radioactive elements can destroy carcinomatous prostatic tissue and adjacent lymphatic tissue without excessive danger to other tissue nearby. Au^{198} was injected into the patients first in the prostate through an open retropubic (Cherny) operative incision and later as a simple perineal injection with multiple needles. Of the 42 patients, 19 died of prostatic carcinoma, the autopsies showing shrinkage of the tumour in only 3 cases. Seventeen of the 20 living have improved, with noticeable softening of the mass and with temporary arrest of the carcinoma in 10, and complete arrest in 7. Best results were seen in well-localized prostatic carcinoma, while large cancerous areas did not respond markedly. Au^{198} does not appear to prolong survival of these patients in most cases but seems more advisable in patients who refuse total prostatovesiculectomy.

TUMOUR-SIMULATING DEFORMITIES AFTER SUBTOTAL GASTRECTOMY

The differential diagnosis between a new or recurrent gastric neoplasm and an operatively produced deformity in a stomach after subtotal gastrectomy is often difficult. In three of four cases presented by Sasson (J. A. M. A., 174: 280, 1960) gastroscopy enabled visualization of the areas of distortion and showed that they were due to plication deformities. The latter caused heavy ridges or bulging folds which simulated tumour growths. In the fourth case the differential diagnosis could not be made, and laparotomy had to be resorted to for diagnosis.

These difficulties could be avoided if, after subtotal gastrectomy, serial gastrointestinal roentgenograms are made routinely before the patient is sent home from hospital or shortly thereafter. This would make x-ray records of surgically created distortions available for future comparison in each case.

THE ROLE OF INTEGRATING SYSTEMS OF THE ORGANISM IN THE DEVELOPMENT OF PATHOLOGICAL PROCESSES

(The Problem of Stress in Pathology)

Referring to the theories of Selye with regard to stress, Gorizontov of Moscow pointed out that the basic concept of stress is not new but that Selye was the first to reveal the importance of the role of endocrine glands, particularly that of the pituitary-adrenal axis, in the stress syndrome. Newly acquired information suggests a need to re-examine Selye's original hypothesis and to attribute increasing importance to the role of the nervous system in production of stress syndromes. Gorizontov thus returned to the classical concepts of Pavlov with regard to the protective effect of acquired conditioned reflexes in the process of adaptation. After reviewing the hypothesis of the adaptation syndrome of Selye, he summarized its application with regard to a variety of illnesses in which the activity of one or all of the corticosteroids is increased as a result of pituitary hyperactivity. He observed that reality is invariably more complicated than theoretical hypotheses would indicate, and expressed the opinion that Selye's concept should not be accepted in its original form without certain reservations. In the first place he felt that it did not attribute due significance to the role of the nervous system. Secondly, he considered isolated or selective overproduction of mineralocorticoids or of glucocorticoids unlikely. Thirdly, he stated that the most active hormone of the adrenal cortex, aldosterone, is not regulated by the pituitary, its production being determined by the level of electrolytes in the blood. All these considerations, however, do not diminish the importance of the hormonal system in the development of pathological processes.

The well-known reflex spasm of vessels after injury, and reflex vomiting after intoxication, are but two examples of the participation of the nervous system in reactions of protection against injury. According to Gorizontov, Selye considered that these processes are not related to the stress syndrome because they are

shortlived and monophasic. In contrast to this concept, he said, Pavlov had illustrated the biological significance of protective blockage in the healing processes, a phenomenon which could not be considered shortlived or monophasic. Furthermore, even in the concept of the pituitary-adrenal system the role of nervous activity via the hypothalamus is considered important. He postulated that the sympathetic nervous system is the site of the earliest changes in the chain reaction of adaptation, in witness whereof he cited the "outpouring of adrenaline" from the adrenals which accompanies this stage of the adaptation reaction. He views this phenomenon as the first of a series of hormonal reactions to stress. The adrenaline thus liberated produces a stimulating effect on the anterior pituitary, as has been demonstrated by Long. There is thus an important interplay between nervous and endocrine systems in the reaction of adaptation. Thus, in certain experiments it has been possible to produce the adaptation syndrome in adrenalectomized animals being maintained on a minimal amount of corticosteroids. Even lymphopenia and atrophy of thymolymphatic organs do not always depend on hormonal influence. In "radiation disease", the greater the dose of radiation, the less significance has the hormonal system in the development of this reaction.

The role of the nervous system has been studied by Pavlov and his school regarding its significance in the origin of pathological processes. In "weak" and "labile" individuals the nervous activity may cause "neurotic" manifestations which would not occur in individuals with a properly balanced nervous system.

Diseases of adaptation occur when a reaction which is mediated through the hormonal system is inadequate and this inadequacy produces a pathological condition. These may occur when there is increased production of hormones resulting in endogenous intoxication with these hormones, when abnormal exchange of hormones and abnormal fixation in the tissues exists, or when there is a disproportion between antagonistic hormones. It can also be the result of a disturbance of the sensitivity to hormones or a disturbance of the function of other systems and organs, such as the nervous system, the renal or the hepatic systems.

Whilst agreeing with Selye that diseases such as Fiedler's myocarditis, necrotizing myocarditis in acute infectious diseases, and subendothelial necrosis, may occur as a result of the combined influence of electrolytes and adrenal cortical hormones as a non-specific reaction to stress, Gorizontov did not agree with the implication that many diseases do not have a specific etiology but may be the result of a "pathogenetic constellation" of multiple etiological factors. He considered that such an approach could constitute a deterrent to "scientific determinism" and the search for causative factors of disease.

The discussion of this paper, presented at a meeting of the Society of "Terapevts" (Internists) in Moscow, was lively. Most speakers, while admitting the importance of the concept of the adrenal-pituitary role in stress, criticized Selye's attempt to create a "generalized theory of medicine". One discussant named Kogan expressed the opinion that Selye's teachings represent a "phenomenon of conditioning" and that such attempts at broad generalization should be criticized "from the point of view of Marxist-Leninist theory".

(Continued on advertising page 13)

OBITUARIES

DR. RAYMOND C. SMITH

AN APPRECIATION

Dr. Raymond Clare Smith died in Sunnybrook Hospital, Department of Veterans Affairs, Toronto, on November 22, after a long illness. In spite of increasing ill health, he persisted in fulfilling his duties at the hospitals to which he was attached and continued his private dermatological practice until two weeks before his death.

Dr. Smith was born in Newmarket, Ontario, in 1915. He attended the University of Toronto Schools and Victoria College, University of Toronto, graduating with the degree of B.A. in 1937. He received the degree of M.D. from that university in 1940. In 1941, after a year of junior rotation internship, he joined the Royal Canadian Air Force, in which he gained the rank of Squadron-Leader. After five years of service to his country he was discharged in 1945. He had become interested in dermatology during his service and determined to specialize in this subject after a further period of training.

In 1946-47 he was a demonstrator in the Department of Pathology and Bacteriology at the University of Toronto. In 1947 he was appointed Junior Demonstrator in the Department of Medicine and spent his time studying dermatology and internal medicine. In 1948 he became a Fellow of the Royal College of Physicians of Canada and was then promoted to the rank of Clinical Teacher which he held until 1954 when he became an Associate in the Department of Medicine. He was an excellent clinical teacher and lecturer, and spent much time and energy in teaching dermatology to the final-year medical students. He had boundless energy and enthusiasm for his work and was very popular with the students. Dr. Smith soon began to do postgraduate medical teaching and was in great demand throughout the province as a lecturer and clinician for the Department of Post-Graduate Medical Education, University of Toronto.

In addition to a busy private practice, he was on the staff of five hospitals and the Workmen's Compensation Board of Ontario, to which he was consultant in dermatology. He managed to spare time for further service in an Auxiliary Medical Unit of the Royal Canadian Air Force, in the Kiwanis Club and the Earls court Children's Home.

His hospital appointments, to each of which he gave enthusiastic service and energy, included the Toronto General Hospital as physician; the Hospital for Sick Children, Toronto, where he was in charge of dermatology from 1954 until his retirement because of ill health in 1960; Sunnybrook Hospital, Department of Veterans Affairs, as consultant, where he was beloved by patients and staff alike; and the Wellesley Hospital, Toronto, and the Ontario Hospital, Orillia, to each of which he was consultant in dermatology.

He remained in the Royal Canadian Air Force Reserve after the Second World War and became a Wing Commander and Officer Commanding 4005 Auxiliary Medical Unit from 1956 to 1959.

He was extremely interested in the Kiwanis Club and was immediate Past-President of the Toronto branch

at his death. He devoted considerable time, effort and enthusiasm to the Earls court Children's Home and was Chairman of the Board of Management from 1956 to 1958. He was Chairman of the Section of Dermatology of the Academy of Medicine, Toronto, at his death. He was a member of the Canadian Medical Association and served on its Central Program Committee for many years. He was also a member of the Ontario Medical Association. To the Canadian Dermatological Association he gave the benefit of his boundless enthusiasm and organizing ability, and was secretary for the combined meeting with the British Association in 1955. For some years he had been a Fellow of the American Academy of Dermatology and Syphilology and regularly attended its meetings.

He was a member of St. George's United Church, Toronto, where he worshipped regularly with his family.

In addition to all these activities he had a full and happy family life. He married Helen Dorothy Henderson in 1941 and they had three children, Ian Raymond, Beverley Joan and Graham Donald, all of whom survive him. The Smith cottage in Muskoka was open house to their multitude of friends. He is also survived by two brothers, Sheldon and Donald, and one sister, Joan (Mrs. Grant Ince).

In the last four years of his life he suffered from increasing ill health, and the marvel is that he had the energy to accomplish so much and do it so well with such indifferent health.

His patients in hospital and private practice adored him and he had the same ready smile, friendly and encouraging word for all. His indomitable courage in the face of a known implacable disease and his determination to fulfil all these duties while any ebbing health remained showed the strength of his character. He will be sadly missed by his colleagues in medicine, by his patients, and by his multitude of friends, but most of all by his bereaved family. To his family are extended the sympathy and condolences of his host of friends, medical and non-medical. N. M. WRONG

DR. RAYMOND C. SMITH

AN APPRECIATION

Raymond C. Smith was a man of many parts. He served his patients, his profession, his church, his community and his family with equal devotion. At all times he displayed drive and enthusiasm. He was always pleasant and had a good word for everyone. Others will record in more detail the diversity of his interests.

He began his career in dermatology at the close of the Second World War, and soon reached the peak of his chosen specialty. For many years he represented the specialty of dermatology on the Central Program Committee of the Canadian Medical Association. He served a term as examiner in dermatology for the Royal College of Physicians of Canada, in which he himself became a Fellow by examination. He had been an active member of the Canadian Dermatological

Association since 1949 and was elected to the office of Vice-President at the annual meeting in 1960.

His colleagues always looked forward to seeing him at meetings and enjoyed his company. Without doubt, he was destined to become one of the leaders in Canadian dermatology. It is with great sorrow that we record his untimely death. His final illness was protracted, yet few other than his closest associates were aware of this. The tremendous fortitude and forthright devotion to duty which he displayed during the past three years stands as an example to all.

R. ROY FORSEY, M.D.,
Historian, Canadian
Dermatological Association.

DR. CLIFFORD V. MULLIGAN

AN APPRECIATION

Dr. Clifford Mulligan was born in 1892, in Omemee, Ontario. He attended primary and secondary schools there, and after a short trial of business entered the Medical School of the University of Toronto. His training, however, was interrupted when he enlisted in the 109th Battalion (Victoria and Haliburton) and went overseas in the First World War. While overseas, he was transferred to the 123rd Battalion of the Royal Grenadiers. His medical course was finally completed at the University of Toronto in 1920. A postgraduate year was taken at the Riverdale Isolation Hospital, after which he returned to Lindsay, for some years of general practice.

He married Isobel Ryley, of Lindsay, in 1923. Their two children, Mary and Flora, were born in Lindsay.

In 1928, further postgraduate work was undertaken in pediatrics at the Hospital for Sick Children, in Toronto, and another year at the Boston Children's Hospital, in 1929. After this, "Mul" practised pediatrics in Toronto, with an appointment at the Hospital for Sick Children.

He enlisted again in the Second World War, and served overseas, this time with the Toronto Scottish. On his return home, he was the medical officer at the prisoner-of-war camp at Monteith. Following the war, he joined the Health Services of the T. Eaton Co. Limited, and became the medical director of the T. Eaton Life Assurance Company, which post he held at the time of his death.

The death of Dr. Clifford Mulligan, on October 30, 1960, brought to a close a life of distinguished service to his country and to his community in the affairs of which he was active. "Mul", with his own inimitable down-to-earth way of thinking, together with his natural charm and eloquence, could handle with ease the most delicate situations. He recognized responsibility and willingly accepted it. His influence will not soon be forgotten. He had a wonderful sense of humour and was an excellent raconteur. He made warm friends among his colleagues and patients, and will be greatly missed by all.

A.W.F.

DR. LAURENT BOUCHARD, aged 32, of St-Honoré, Que., died suddenly November 5 when he touched a high-voltage wire while attempting to assist his brother after an automobile accident.

A graduate of Laval University in 1954, Dr. Bouchard is survived by his widow and two children.

DR. JACK BRENER, 56, head of the department of anesthesia at Misericordia Hospital, Winnipeg, died on November 13 after a long illness. He graduated in 1928 from the Faculty of Medicine, University of Manitoba, and was certified in anesthesia by the Royal College of Physicians and Surgeons of Canada.

Dr. Brener is survived by his widow, two sisters and a brother.
R.M.

DR. CLARENCE E. BROWN, aged 74, died in Shaughnessy Hospital, Vancouver, on August 6, 1960.

He was for many years a prominent internist in Vancouver, and was intimately connected with St. Paul's Hospital, where he was in charge of the electrocardiographic department. He had a high reputation with his colleagues on account of his clinical acumen and diagnostic ability.

He graduated from the University of Western Ontario in 1909, and spent two and one-half years on the staff of New York hospitals, moving to Vancouver in 1920 after a term of service in the C.A.M.C. in England and France.

DR. J. EUGENE DIONNE, of Ste-Marie, Que., died November 3, aged 87. He graduated from Laval University in 1900.

Dr. Dionne is survived by his widow, two sons, one of whom is Dr. Louis-Phillippe Dionne, and two daughters.

DR. E. MAITLAND HORTON, aged 87, died September 18 at his home in Enterprise, Ont. Born there, he graduated from the University of Toronto in 1910 and practised in Enterprise for 45 years.

DR. OMER MANSEAU, aged 53, died in Montreal October 24. He was a graduate of the University of Montreal in 1932.

Dr. Manseau is survived by his widow and one daughter.

DR. JOHN T. O'GORMAN, aged 67, died October 23 at his home in Eganville, Ont. A graduate of the University of Toronto in 1928, he practised in Pembroke and Eganville, and served overseas for four years during World War I.

Dr. O'Gorman is survived by his widow and two sons.

DR. HOWARD LESLIE READ, aged 72, died October 24 in Regina. Born in Marshalltown, Iowa, he received his medical degree from Iowa State University in 1917 and did postgraduate work in pediatrics in San Francisco. He served with the American Army Medical Corps and began practice in Earl Grey, Saskatchewan, in 1919. During the Second World War he was a member of the Canadian Army Medical Corps and for many years was Regina's official examiner for the boxing and wrestling commission.

Dr. Read is survived by his widow, two sons and a daughter.

DR. JOSEPH J. WILLIAMS, aged 91, died November 11 in Wellesley Hospital, Toronto. Born in Tottenham, Ont., he graduated from the University of Toronto in 1892 and practised in Simcoe County. He held appointments as superintendent of the Ontario Hospitals at Woodstock and Hamilton.

Dr. Williams is survived by two daughters.

BOOK REVIEWS

PRACTICAL CLINICAL MANAGEMENT OF ELECTROLYTE DISORDERS. William J. Grace, Director of Medicine, St. Vincents Hospital, New York. 132 pp. Illust. Appleton-Century-Crofts, Inc., New York, 1960. \$4.95.

Clinical syndromes relating to electrolyte disorders are described by the author in a manner which presents them in a form which may be most readily understood by clinicians and students. Dr. Grace describes electrolyte disorders with a minimum of physiological and biochemical background and an ideal amount of clinical description and application. He uses case histories to illustrate specific points and thereby makes it easier for the reader to grasp what is being described and also what may well apply to his own practice. This is occasionally done in other texts on the subject but never so concisely as it is here. It is the reviewer's opinion that physicians and surgeons alike would be well advised to have this text readily at hand to help them handle electrolyte problems. Guesswork, which occasionally enters the picture as the average clinician tries to deal with electrolyte problems that do not arise frequently enough to be readily retained in his mind, would be done away with. This small handy text accomplishes what many larger books have failed to do in the past.

ESSENTIALS OF PHARMACOLOGY. Frank K. Oldham, F. E. Kelsey and E. M. K. Geiling. 396 pp. Illust. 4th ed. J. B. Lippincott Company, Philadelphia and Montreal, 1960. \$7.75.

In the fourth edition of this popular short text, the authors have adhered to the original plan of the first edition. The book is intended to be used as an introductory text in pharmacology. It is useful for medical students beginning their course in pharmacology, but some professors of pharmacology would require their students to know more about various drugs than is given in this short book. The book has been found useful by older students and graduates in preparing themselves for enabling examinations in pharmacology. Older physicians in medical practice will find that it enables them to get a proper perspective on recent trends in drug therapy. The latest edition is particularly useful in this respect. It contains brief descriptions of newer groups of drugs such as hallucinogens, tranquillizers, monoamine oxidase inhibitors, the chlorothiazides, carcinolytic agents, and recent anti-infectives. Laws and legal regulations pertaining to drugs described in the book are those in force in the United States of America.

RADIOLOGY AS A DIAGNOSTIC AID IN CLINICAL SURGERY. Howard Middlemiss. 147 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. \$9.00.

This is an unusual, short book intended for surgeons and written by a radiologist. The emphasis is on clinical problems, and the author has selected his subjects from those on which his surgical colleagues have consulted him in daily practice in a busy teaching hospital. He has particularly attempted to emphasize the scope and limitation of radiology in regard to various surgical problems. The need for consultation between the radiologist and surgeon is stressed. The author also

points out the often forgotten fact that the radiologist will usually carry out a much more successful examination if he is made aware of the clinical problem beforehand. The examination can then be planned in a much more intelligent manner.

No attempt has been made to cover radiology in minute detail. However, sufficient material is included to give a broad outline of most general surgical problems. The book should be informative and helpful for young surgeons and surgical residents and also for those who intend to go into general practice. It is doubtful if it will have much impact on older surgeons who are set in their ways, but most of them could derive some benefit from it if they read it carefully.

ELECTRON MICROSCOPY OF THE CARDIOVASCULAR SYSTEM. Bruno Kisch. 164 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. \$8.25.

The title of this short monograph is misleading, since the book deals not with the cardiovascular system, but with the myocardium. There is only a brief description of endocardial cells, capillaries and cardiac nerves.

With the exception of a few electron micrographs, the quality of pictures is poor. They are not even up to the standards of the average present-day publications in the field of electron microscopy.

The main topics discussed deal with the general structure of muscle fibres; sarcolemma; myofibrils; myofilaments, cross-striation, sarcosomes and the sarcosome theory of function of the heart; membranes and other structures within the cardiac muscle fibre; intercalated discs; nuclei, interstitial cells, endocardial cells, capillaries, cardiac nerves and the mechanisms of pain in angina pectoris, and the mechanism of axon reflexes.

There is no description of the fine structure of the endocardium and pericardium, of the interstitial connective tissue of the myocardium, of the coronary arteries or of other vessels.

GENERAL ANAESTHESIA FOR DENTAL SURGERY. R. S. Walsh, First Assistant, Department of Anaesthetics, St. George's Hospital, London. 94 pp. Illust. J. B. Lippincott Company, Montreal, 1960. \$3.75.

This book covers well the field of anesthesia designated in its title. Many Canadian anesthetists are never called upon to attend a dental patient, so that such a book is of limited interest in this country. However, it could be read with advantage by all those who may be involved in dental operations, major and minor.

The author's descriptions of hazards and accidents recall vividly to the reader's mind episodes of past experience, and make for realization of the experience from which Dr. Walsh writes. The treatise is brief but adequate.

The mention of two newer methods of administering nitrous oxide, entitled amnalgasia and pre-oxygenation, are cheering to the anesthetist who still worries about the fact that "hypoxia of greater or less severity accompanies every dental 'gas'."

THE CANADIAN MEDICAL ASSOCIATION

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The appointment is a full-time one which will require residence in the Toronto area. The salary will be in accordance with the candidate's qualifications and experience. There is a contributory pension plan, and group hospital and health insurance is available.

Candidates are asked to apply in writing, giving full particulars and enclosing a recent photograph, to: The Editor, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

MANUAL OF BLOOD MORPHOLOGY. L. Schudel. 53 pp. Illust. 9th ed. J. B. Lippincott Company, Philadelphia and Montreal, 1960.

This manual is written in English, French, and German. It is concise and elementary. It should prove useful in the initial training of hematological technicians and to second-year medical students in their introduction to hematology. It should be helpful also to interns and general practitioners for reference to the illustrations as an aid in morphological identification. It is of no value to the advanced student, technician, or hematologist.

The illustrations are its best feature, and appear to be water-colour illustrations of the various cell types found in the blood and bone marrow, in health and in disease. These illustrations are well executed and excellently reproduced.

The tables of normal values are, at best, only approximately correct, and some of the values given are in error; for example, the normal value for reticulocytes is given as 5 to 10%. Consequently, these tables for normal quantitative values are best disregarded in favour of reference elsewhere. Only a few techniques are given, and there is no effort to compare the various techniques for a procedure (e.g. various methods of performing platelet counts) or to detail the various sources of error.

In summary, this manual has its greatest value in the illustrations, which can be used for reference purposes for beginners in hematological morphology.

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GENERAL PRACTITIONER with previous experience in industrial medicine wishes to undertake medical work in insurance, industrial or other fields in or near Toronto. Mornings available. Reply to Box 198, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

GENERAL SURGEON, Canadian and American trained. FRCS and American Board eligible. Desires to associate with an individual group or clinic. Available immediately. Reply to Box 199, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

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25-YEAR-OLD British graduate, who has just completed junior internship, has 3-4 months to spare, is looking for position as locum in general practice, available from January 1st. Further details upon request. Reply Dr. J. J. MacMahon, St. Joseph's Hospital, London, Ontario.

DOCTOR, age 35, with European certificate in surgery, fully licensed in Canada (L.M.C.C.), American Board and F.R.C.S.—orthop. (fall 1960), eligible seeks suitable position (hospital staff appointment, assoc. with another orthopedist) after Christmas 1960. Reply to Box 213, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

INTERNIST, Canadian, 31, four years' postgraduate training. Eligible for FRCP examinations. Wish to locate in urban area, preferably Ontario in industrial, institutional, insurance or private practice. Reply to Box 214, CMA Journal, 150 St. George Street, Toronto 5, Ontario.

MEDICAL NEWS in brief

(Continued from page 1441)

\$25,000 GRANTED FOR BIRTHS STUDY

The American Medical Research Foundation has granted \$25,000 to launch a pilot program which will provide detailed information on the birth of 100,000 babies in 100 hospitals, beginning January 1, 1961. The program's aim is to reduce infant mortality and morbidity. A five-year program involving a minimum of one million births is planned to follow the pilot study.

Dr. Sydney H. Kane, Philadelphia, will serve as project director. He will be assisted by an advisory committee headed by Dr. Philip Barba, Philadelphia. Dr. Barba also is chairman of AMA's Committee on Maternal and Child Care which carried out preliminary work for the program.—*AMA News*, October 31, 1960.

TRAVEL GRANT APPLICATIONS, SECOND INTERNATIONAL CONFERENCE OF HUMAN GENETICS

The Second International Conference of Human Genetics will be held in Rome, Italy, on September 7-12, 1961. Information and registration forms may be obtained from the Secretariat of the Second International Conference of Human Genetics, Istituto "G. Mendel", 5 Piazza Galeno, Rome. The American Society of Human Genetics has been granted funds by the National Science Foundation and by the U.S. National Institutes of Health for the support of travel of a limited number of the American delegation to the Conference. The Secretary of the American Society of Human Genetics is mailing application forms to members of the Society. Nonmembers may obtain forms from Professor C. P. Oliver, Department of Zoology, University of Texas, Austin. The amounts granted will depend on the number of applications, but probably will not exceed the amount required for air tourist round trip fare to Rome. It was decided by the Society that maximum travel grants would be awarded to persons invited by the Secretariat of the Conference to participate in Symposia and to ap-



PHYSICIANS Ontario Mental Health Service

A training program leading to eligibility for certification by examination in the specialty of psychiatry by the Royal College of Physicians and Surgeons (Canada) is offered while serving in the Ontario Mental Health Service.

Applicants are required to be in possession of a licence to practise medicine in the Province of Ontario. The starting salary is \$4,800 per annum with annual increments for satisfactory service.

Physicians are classed as Residents in Psychiatry. The training program leading to eligibility to sit the Certification Examination in Psychiatry by the Royal College of Physicians and Surgeons (Canada) is four years in duration. The usual plan is to place physicians during the first year in an Ontario Hospital approved by the Royal College of Physicians and Surgeons for training specialists in psychiatry. The second and third year is spent on secondment to the university of the applicant's choice in Ontario offering graduate training in psychiatry, subject, of course, to acceptance by the university. The universities in Ontario offering such training under this plan are Queen's University, University of Ottawa, University of Toronto and University of Western Ontario.

Physicians on successful completion of the University course and transfer to an Ontario Hospital are reclassified and, on recommendation, increased to a minimum of \$7,800 per annum with annual increments of \$400 per annum for satisfactory service. Successful completion of the Certification Examination in Psychiatry by the Royal College of Physicians and Surgeons (Canada), leads to immediate reclassification as a Medical Specialist with salary increase to \$10,000 per annum, with annual increments at the rate of \$500.

Superannuation benefits. Annual vacation. Sick leave gratuity. Living accommodation available in some hospitals at nominal rental.

Following certification as a specialist, a wide variety of positions are available as senior staff psychiatrists on hospital duty, in charge of mental health clinics, or in charge of a community psychiatric clinic in public general hospitals, or out-patient departments, etc.

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Ontario Department of Health,
Parliament Buildings, Toronto

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Hon. Matthew B. Dymond, M.D. C.M.
Minister

plicants whose abstracts are approved by the Society Committee on Program Arrangements. Applicants, other than participants in Symposia, who plan to present scheduled scientific papers at the conference are to submit a carbon copy of their abstract to Dr. F. C. Fraser, Department of Genetics, McGill University, Montreal, Canada. The abstracts must arrive on or before April 1, 1961. Persons who will not present papers at the Conference may apply for partial travel assistance; the procedure is explained in the application form.

NEW HOME OF ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The new home of the Royal College of Obstetricians and Gynaecologists in London, England, was officially opened on July 13, 1959, by Her Majesty the Queen. Three Commonwealth physicians were invited to present papers on pelvic cancer: Dr. A. D. Campbell of the Montreal General Hospital; Dr. W. G. Cosbie of the Toronto General Hospital; and Dr. A. Hill of Melbourne, Australia.

At a second session the chairman was Dr. A. B. Nash of Victoria, B.C., his subject being "The use and abuse of antibiotics". Dr. T. F. Corkhill of Wellington, New Zealand, acted as chairman of the session dealing with "Hemolytic Disease of the Newborn".

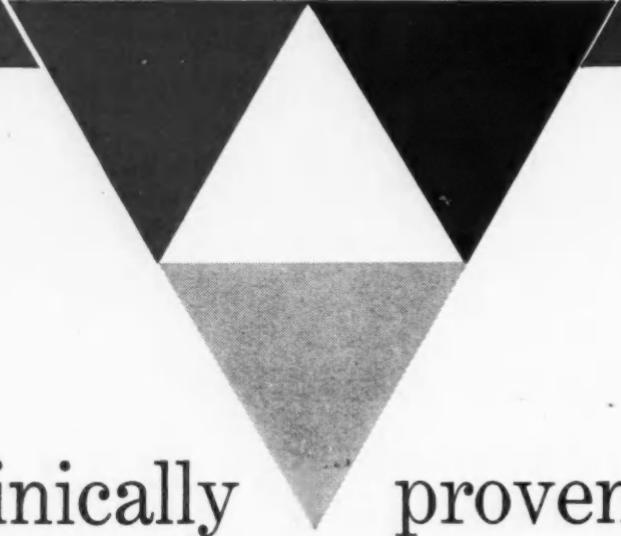
Some 350 of the leading obstetricians and gynecologists of the world attended the opening of the new building.

The Hall of the College was donated and furnished by Lord Nuffield. The Royal College of Physicians and Surgeons of Canada also presented appropriate donations. There were also many gifts from the parts of the commonwealth.

COURSE IN SURGERY OF THE HAND

A five-day full-time course on Surgery of the Hand will be offered by the New York University Medical Center from March 6-11, 1961, under the direction of William T. Medl, F.A.C.S., and Thomas D. Rees, F.A.C.S. The course is

(Continued on page 15)



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Terrell, W. et al: The Newer Sulfonamides, M. Clin. North America, March, 1957, p. 539.

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MEDICAL NEWS in brief

(Continued from page 13)

designed mainly for general, orthopedic, plastic and industrial surgeons.

The sessions will consist of practical demonstrations, lectures and panel discussions by members of the New York University faculty and a visiting faculty of eminent specialists in surgery of the hand. All facets of modern hand surgery, including anatomy, physiology, diagnosis, surgical techniques and management of hand lesions, will be covered.

The guest faculty will include: Robert A. Chase, Yale University School of Medicine; Martin A. Entin, McGill University Faculty of Medicine; Jerome Gelb, Kessler Institute; J. William Littler, Columbia University College of Physicians and Surgeons; Erle A. Peacock, Jr., University of North Carolina School of Medicine; Lee Ramsay Straub and T. Campbell Thompson, Cornell University Medical College; Cdr. William C. Trier, M.C., U.S.N., Philadelphia Naval Hospital; and William L. White, University of Pittsburgh School of Medicine.

The class is limited to 40 participants and the tuition is \$125. For applications write to the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.

INTERNATIONAL SOCIETY FOR CLINICAL AND EXPERIMENTAL HYPNOSIS

The Canadian Division of the International Society for Clinical and Experimental Hypnosis invites application for Associate and Full Membership in the Canadian Division. Applicants must hold an M.D., D.D.S., or Ph.D. degree from recognized universities and have had some experience in the use of hypnosis in the field of their competency.

The Canadian Division is one of 25 Divisions of the International Society for Clinical and Experimental Hypnosis representing 25 countries throughout the world. Applicants should write to Dr. Morton Korenberg, Medical Arts Building, 1538 Sherbrooke St. West, Montreal, giving full particulars of training and experience in the field of hypnosis.

THE SUPPLY AND DISTRIBUTION OF DOCTORS IN SWITZERLAND

The total number of medical students in Swiss universities in the year 1959-1960 was 3015, of whom only 1831 were of Swiss nationality. This represented a slight decrease from the previous year. The decrease affected only male students, the number of female students being slightly increased. Compared with the year 1943-1944, the current medical school population in Switzerland showed a 20% decrease. The number of future doctors is thus not keeping pace with the increase in the national population. The total number of doctors in Switzerland at present is 7928. In private practice there are 4908, of whom 2274 are general practitioners and 2634 certified specialists. There are 233 doctors in civil service or on full-time salary, and 2301 assistants and interns. Of all practising doctors, some 30% (1480) perform their own dispensing; 312 work in hospitals on a full-time basis. Female doctors total 985, of whom 407 are practising, 17 are employed and 409 are interns. The number of citizens per practising doctor fluctuates widely in the various cantons (from 666 in Geneva to 2720 in Appenzell), and averages 1074 persons per doctor. —*Schweiz. Aerzteztg.*, 41: 595, 1960.

ATTENTION EXHIBIT CHAIRMEN

Medical Exhibitors Association is now compiling its 1961 Tentative Schedule of Conventions for its members — which comprise the majority of exhibitors at medical and allied meetings — and would like those officers concerned with planning the details for next year's meeting to forward details. This applies particularly to exhibit chairmen.

Information dealing with the location of the meeting, name of hotel or hall, size and cost of booths, society member in charge, 1960 attendance and anticipated 1961 attendance, and other pertinent details, should be sent to Douglas R. Weston, Executive Secretary, Medical Exhibitors Association, 37 King Street East, Toronto 1, Ontario.

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The sulfas — for a while displaced by antibiotics — are now coming into their own again as drugs of choice for many infections seen in practice today. More and more, and quite properly, the use of antibiotics is being reserved for infections not responsive to treatment with other drugs.

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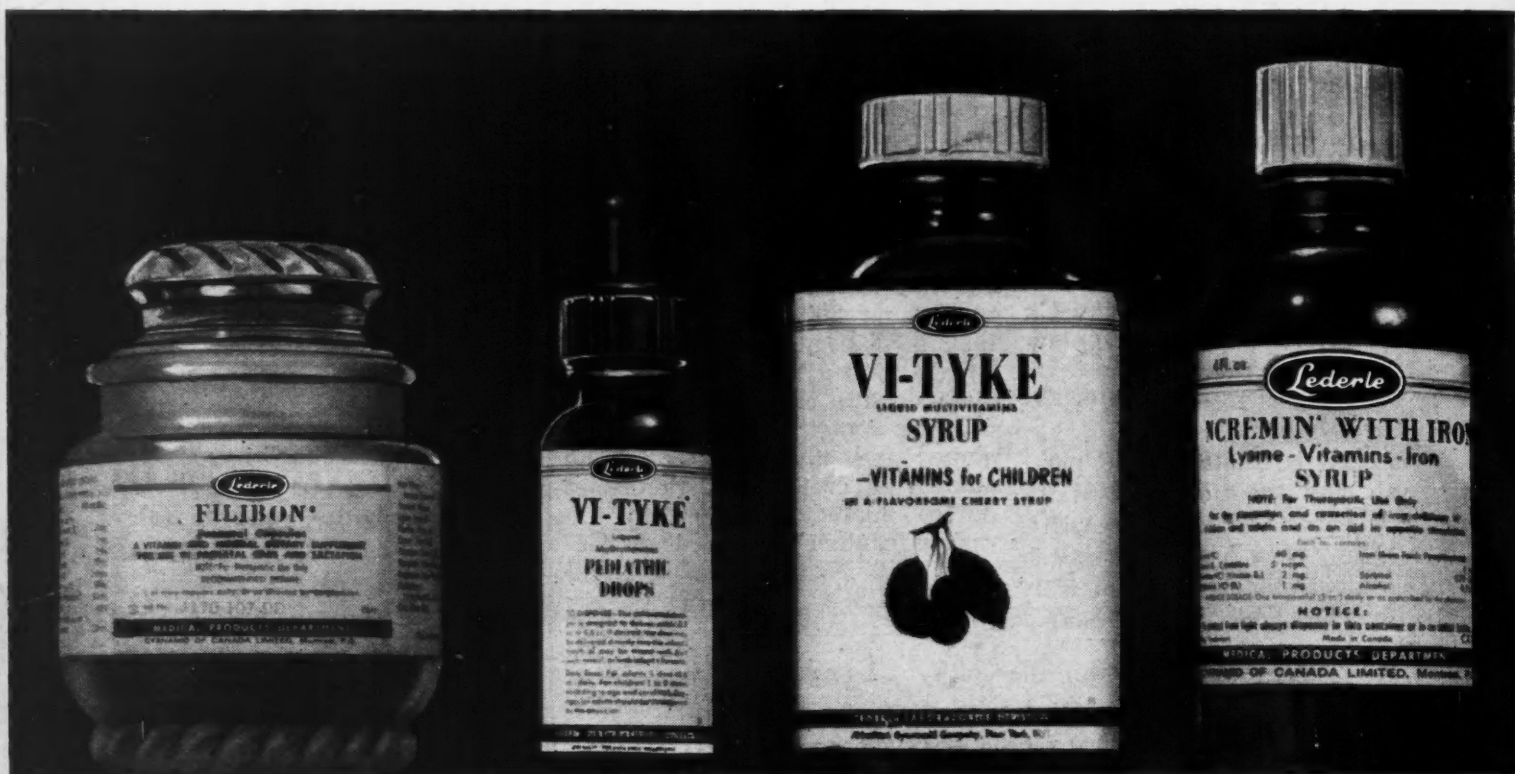
INFANT DROPS. A multi-vitamin preparation perfect for all infants. Dose: 5 to 10 drops daily.

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